STERIC EFFECTS IN

CARBOHYDRATE CHEMISTRY

by

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CONTENTS

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PART I

THE RELATIVE RATES OF FORMATION OF 3,6-ANHYDRO-COMPOUNDS : AN INVESTIGATION OF STERIC INTERACTIONS.

TABLE OF CONTENTS FOR PART I

The Relative Rates of Formation of 3,6-Anhydro-compounds : An Investigation of Steric Interactions.

I N T R O D U C T I O N

The great value and wide range of application of conformational analysis in sugar chemistry has been realised for some time.[1-6] Examples of its use are the interpretation both of positions of equilibria (e.g. of mutarotation[1] and the formation of 1,6-anhydro-aldoses from the free sugars[1,7]) and of the relative rates of reaction of stereoisomeric compounds (e.g. glycoside hydrolysis,[6] and periodate oxidation[5,13] of various types of sugar derivatives).

Notwithstanding the slight distortion of the pyranose sugar ring caused by the shortness of the C-O bond relative to the C-C bond, the principles employed in the conformational analysis of six-membered alicyclic rings[8] can be extended to the carbohydrates.

These principles are:

1. Six-membered rings generally take up strainless, puckered chair forms. The result of this is that substituents can have an "axial" or "equatorial" orientation, depending on the direction of the substituent-ring bond relative to the axis of the ring. (See Figure 1).

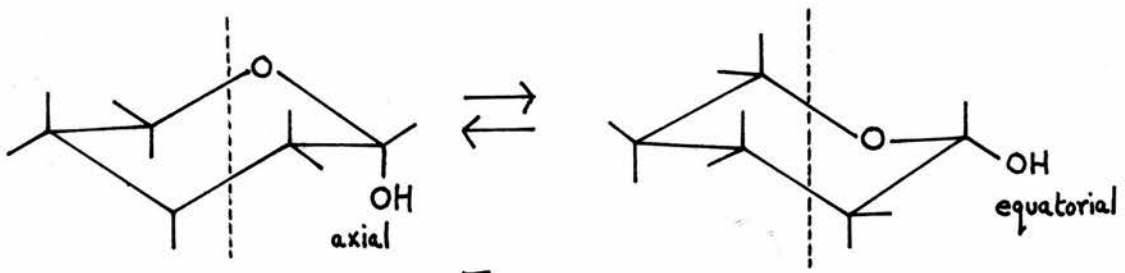


Fig. 1

The two possible chair forms are interchangeable, although separated by a low energy barrier, and exist in equilibrium with each other. Boat forms (e.g. Figure 2) are also free from angle-strain, but normally chairs are preferred energetically.

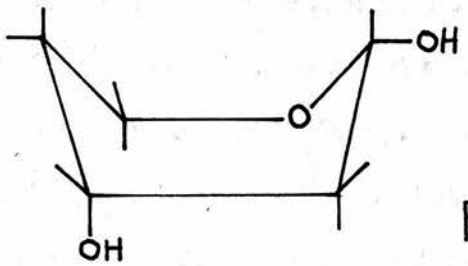


Fig. 2

2. In general the steric (i.e. non-bonded) interactions encountered by a substituent are greater when it has an axial orientation than when it is equatorial.

3. The preferred, i.e. most stable conformation of a molecule is usually that possessing the greatest number of substituents oriented equatorially, since in this way the steric interactions are minimised.

The aim of the investigation of which the present work is a part is to examine and assess, if possible on a quantitative basis, the various factors affecting reactivities in carbohydrate chemistry. Considerable progress has been made already in assessing the magnitudes of steric interactions in cyclohexane chemistry,[9] including that of the inositols.[10] However, comparatively little quantitative work has been done in carbohydrate chemistry, although Lemieux, in preliminary communications,[11,12] has estimated the interactions in sugar

acetates by the use of nuclear magnetic resonance spectroscopy in measurements of anomeric equilibria. An attempt by Barker and Shaw[13] to calculate the relative magnitudes of steric interactions from the overlap of van der Waals radii is also of interest.

In the work described here, the approach has been to examine the alkaline cyclisation of several pyranose monosaccharide 6-p-toluenesulphonates (tosylates) to the 3,6-anhydro-compounds. The reason for choosing this reaction, which is the standard method of preparing these derivatives,[14] is that a change of the conformation of the molecule is necessary before cyclisation can take place. It is definitely known that in solution the preferred conformation of most pyranose sugar derivatives is the "Cl". (See Figure 3)[1,15,16]

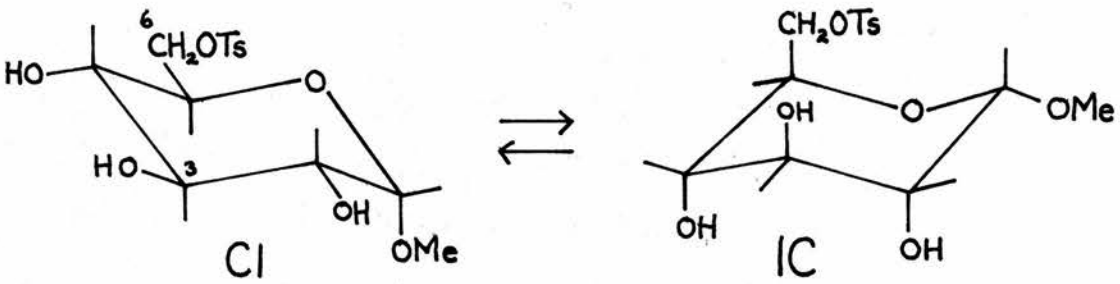


Fig.3

Hence in those sugars in which it is possible to have ring-closure, viz. the ones having the 3-hydroxyl group on the same side of the ring as the 6-carbon atom, the reacting groups are equatorially

oriented, and so are too far separated to react. But after a change to the less favoured chair conformation (1C) these groups are both axial and are suitably placed for ring-closure. The relative rates of reaction of stereoisomeric 6-tosylates should therefore depend on the relative differences between the non-bonded interactions in the two chair conformations.

The above reaction has already been studied from a quantitative point of view by R. Baker[17] (unpublished work done in the Chemistry Department at Edinburgh). In the present work, the conditions of the reaction have been modified, and the work has been extended to cover a wider range of compounds and a new solvent system.

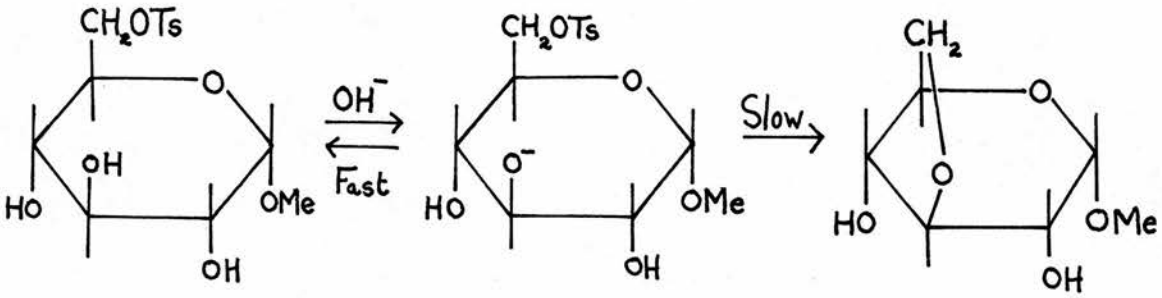
DISCUSSION

A - Kinetic and Conformational Aspects

1. The Kinetics of Cyclisation of Sugar 6-Tosylates to 3,6-Anhydro-derivatives

Formation of 3,6-anhydro-compounds by the action of alkali on the 6-p-toluenesulphonates (tosylates) of hexopyranose derivatives is an intramolecular S_N2 reaction, in which the 3-hydroxyl group of the sugar is ionised by the base; the resulting alkoxide ion makes a nucleophilic attack on $C_{(6)}$ and tosylate ion is produced. (See Figure 4).

Fig. 4



Methyl α-D-glucopyranoside 6-tosylate

Methyl 3,6-anhydro-α-D-glucopyranoside

The rates of cyclisation of the 6-tosylates of 1,5-anhydro-D-glucitol, 1,5-anhydro-2-deoxy-D-arabino-hexitol, methyl α-and β-D-glucopyranoside and methyl α- and β-D-galactopyranoside have been studied by R. Baker[17]. It was found that the reactions could be conveniently followed spectrophotometrically, since at the wavelength

265 mμ the absorption of the tosylate ion is much less than that of tosyl esters. (For details, see Experimental, 5.).

The reactions were carried out in a large excess of sodium hydroxide, so that the concentration of alkali was practically constant - under these conditions first-order kinetics were observed. The cyclisation of 6-tosylates is formally similar to the cyclisation of ethylene chlorohydrin with alkali to give ethylene oxide, a reaction which is usually considered[18a] to be second-order, i.e. first-order with respect to the chlorohydrin and to the base.

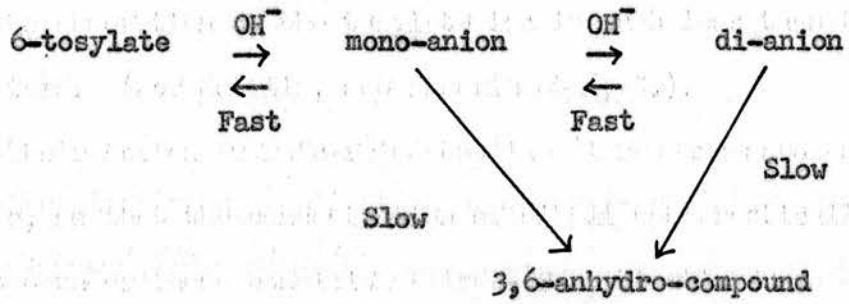
It was therefore expected that the first-order rate constants (k_1) for the cyclisation of the tosylates would be directly proportional to the hydroxide concentration. However, Baker found that for the 6-tosylates of 1,5-anhydro-D-glucitol and of methyl α- and β-D-glucopyranoside the ratio $k_1/[OH^-]$ was not constant, but increased considerably as the hydroxide concentration was increased. Hence the order with respect to base is greater than one (less than two, however). It was shown that this behaviour was not due to a salt effect, since it persisted even when a medium of high and constant ionic strength (3M, using sodium chloride) was used. (It is of interest that recent work[19] has shown that the cyclisation of ethylene chlorohydrin is not strictly first-order with respect to hydroxide concentration either).

The unexpected results with the 6-tosylates mentioned can be explained by assuming that the cyclisation reaction occurs not only via the 3-mono-anion mentioned earlier, but also (to some extent) via di-anions. The following reaction scheme was postulated:

Table 1. Statistically Determined Data for Cyclisation of Monosaccharide 6-Tosylates with Excess Sodium Hydroxide at Various Concentrations, at Ionic Strength 3 M, at 20°.

Compound	$10^4 k_2$	$10^4 k_3$	Z
1,5-anhydro-D-glucitol 6-Ts	102	866	3.3
1,5-anhydro-2-deoxy-D-arabino-hexitol 6-Ts	95.0	-	-
Me α-D-glucopyranoside 6-Ts	10.0	134	2.3
Me β-D-glucopyranoside 6-Ts	6.77	57	2.1
Me α-D-galactopyranoside 6-Ts	78.8	110	2
	79.3	177	3
Me β-D-galactopyranoside 6-Ts	55.1	92	2
	55.2	143	3

k_2 is in l./mol./sec. Me = methyl Ts = tosylate



It can be shown that this leads to the relation

$$k_1/[OH^-] = \frac{k_2 + k_3[OH^-]}{1 + Z[OH^-]} \qquad (1)$$

between the experimental first-order rate constants (k_1) and the hydroxide concentration. In this equation k_2 and k_3 are rate constants representing cyclisation via the mono- and di-ions respectively, and Z is related to the ionisation constant of the sugar. The experimental results for the three glucopyranose tosylates mentioned earlier could be fitted to the above equation, and by using a statistical procedure, Baker calculated values for k_2, k_3 and Z, which are shown in Table 1. For the methyl α- and β-galactoside 6-tosylates, $k_1/[OH^-]$ showed only a slight increase with increasing hydroxide concentration, and it seems probable that the reason for this is that $k_3/k_2 \simeq Z$ for these compounds. The values of k_2 and k_3 shown in Table 1. for the galactosides were calculated by using assumed values (2 and 3) of Z similar to those obtained for the glucose derivatives, and it is clear that the value of k_2 is practically unaffected by the assumptions made about Z. (For 1,5-anhydro-2-deoxy-D-arabino-hexitol 6-tosylate $k_1/[OH^-]$ was independent of $[OH^-]$, i.e. the cyclisation of this compound was

strictly second-order, and the value given for k_2 is the average of the observed values of $k_1/[OH^-]$).

From the above discussion it is clear that the values of the first-order rate constant k_1 for cyclisation of the various compounds at one particular hydroxide concentration would not really be suitable for conformational comparisons between the compounds, since k_1 is a composite quantity. From the conformational point of view, the most suitable quantity to take for the purpose is k_2, the rate constant representing reaction *via* a mono-ion, and this was the quantity used by Baker as the basis for conformational discussions. However, the aim of the present work was to examine a much wider range of compounds and to study the effects of altering the solvent, and in these circumstances an approach depending on the rigorous determination of k_2 for the various compounds was considered undesirable. The main reasons for this were that the determination of k_2 is extremely tedious and that the necessity of maintaining a constant, high ionic strength precludes the use of media containing large amounts of organic solvents.

In the present work the rates of cyclisation (k_1) have therefore been measured at only one hydroxide concentration, *viz.* 0.02 N. Baker's work has shown that at this very low concentration the cyclisations proceed mainly *via* the mono-ion, since in every case the value of $k_1/[OH^-]$ was then within 10% of the corresponding value of k_2 obtained statistically. This being so, the values of k_1 obtained in 0.02 N-base are a suitable basis for conformational comparisons. This approach was used by Bender and Thomas[20] in the study of the

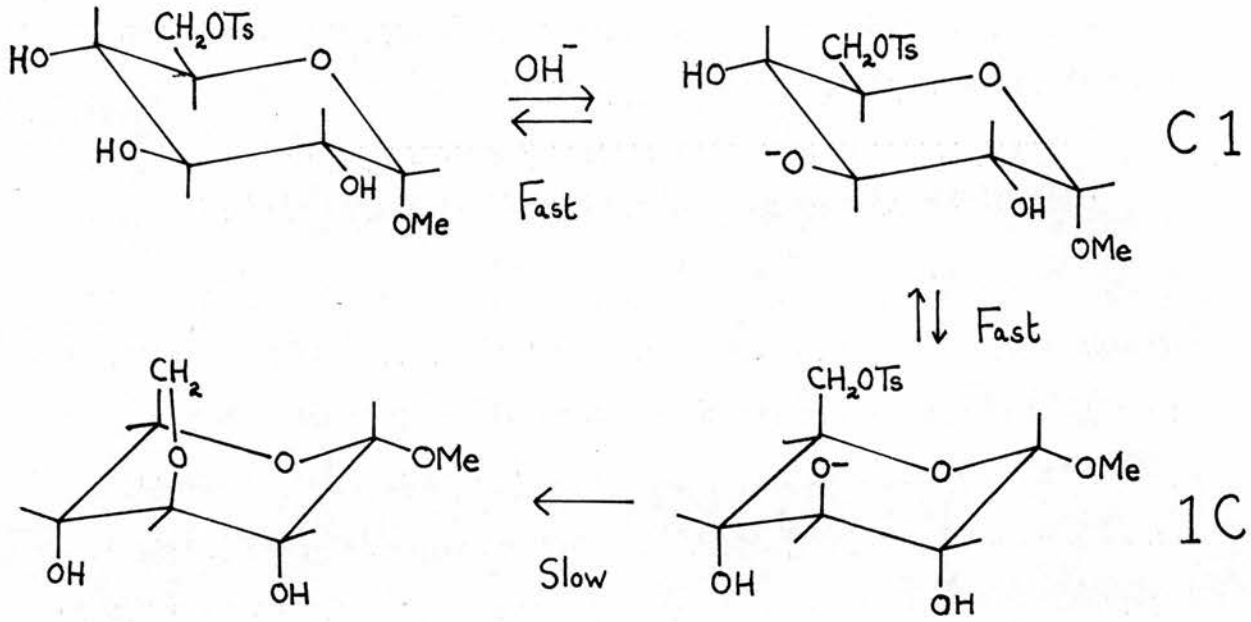
hydrolysis of acetanilides in alkali, which reaction also involves both mono- and di-ions. This particular concentration of base was also convenient in that it was low enough to permit the measurement of the most reactive compounds involved.

The detailed procedure used in the rate measurements is described in the Experimental (Section 5.) and the preparation of the required 6-tosylates is discussed in Part B of this Discussion. For the six compounds which are not mentioned in the Experimental, samples were used which had previously been made by R. Baker. The concentration of tosylate used was 0.001M and the resulting excess of alkali was sufficient to give first-order kinetics, within the limits of experimental error. (See Appendix II). The average first-order rate constants (k_1) obtained for the twelve tosylates included in the present study are shown in Table 2. below. It may be noted that the relative magnitudes of the rate constants found for the compounds already examined by Baker are very similar to those obtained by him (Table 1.).

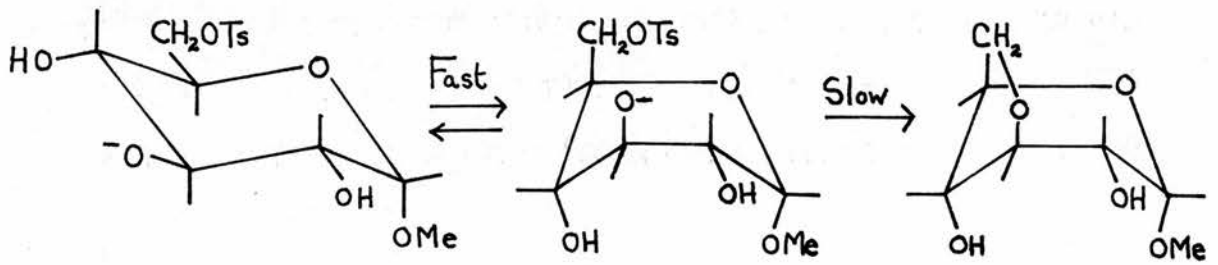
2. Interpretation of the Relative Rates of Cyclisation in Alkali of a Number of Monosaccharide 6-Tosylates.

(a) The conformation of the transition state.

Taking account of conformations, the reaction sequence for formation of methyl 3,6-anhydro-α-D-glucopyranoside may be written as:



An alternative possibility to the conformational change (C1 - 1C) shown in this scheme is that only one end of the molecule should change its shape in the rearrangement which must take place before cyclisation can occur. We would then have, for the formation of methyl 3,6-anhydro-α-D-glucoside:

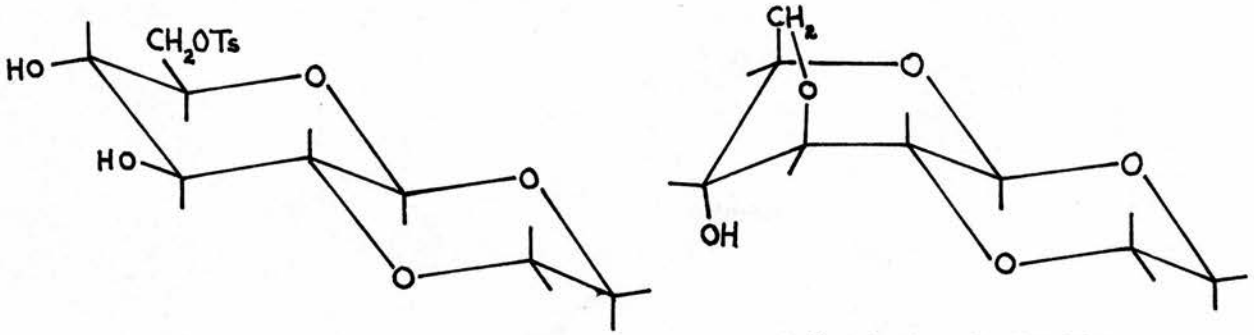


Clearly in this case the boat form of the transition state and of the 3,6-anhydro-product is highly unfavoured, owing to the severe "bow

and stern" interaction between the glycosidic methoxyl and the 4-hydroxyl group. But in other cases the possibility of a boat transition state cannot be excluded with certainty.

Circumstantial evidence against this type of transition state has been summarised by Baker[17] in particular, the constancy of the ratio of the rates of cyclisation of the α- and β-anomers of methyl D-galacto- and gluco-pyranoside 6-tosylates (which was confirmed in the present work for the corresponding anomeric 2-deoxy-glycoside 6-tosylates) suggests that boat forms, which would be more favoured in the galactose series, do not play a significant part.

In connection with the possible participation of boat forms, the reaction of 1,2-O-ethylene-β-D-glucopyranose 6-tosylate with alkali was examined, since this compound (shown in the Figure) can



3,6-anhydro-derivative

cyclise only in the boat conformation (owing to the rigidity of the trans-ring juncture at $C_{(1)}$ and $C_{(2)}$). It is significant that no reaction occurred under conditions in which other 6-tosylates cyclise rapidly. Under vigorous conditions, several products were formed (see Discussion B, 2. and Experimental, 3.) and it is clear that 3,6-

Table 2. First-order Rate Constants (Average) for Reaction of 6-Tosylates (0.001M) with 0.02N-Sodium Hydroxide at 25°

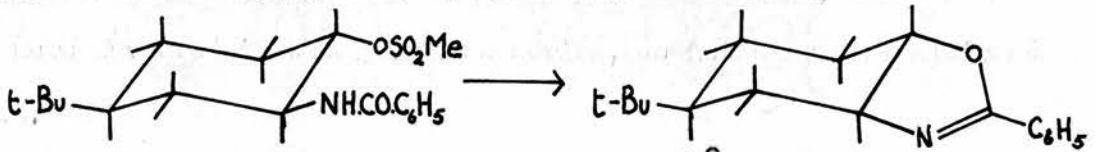
Compound	Half-life (min.) in water	Rate constants (k_1) in units 10^{-5} sec.$^{-1}$	
		Water	50% Aqueous dioxan
1,5-anhydro-D-glucitol 6-Ts	23	51.4	107
1,5-anhydro-2-deoxy-D-arabino-hexitol 6-Ts	23	50.5	74.5
Me α-D-glucopyranoside 6-Ts	230	5.00	9.89
Me β-D-glucopyranoside 6-Ts	345	3.33	8.68
Me 2-deoxy-α-D-glucopyranoside 6-Ts	42	27.3	33.4
Me 2-deoxy-β-D-glucopyranoside 6-Ts	57	20.4	27.7
1,5-anhydro-D-galactitol 6-Ts	2.0	581	1210
1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-Ts	7.5	157	373
Me α-D-galactopyranoside 6-Ts	27	42.6	78.3
Me β-D-galactopyranoside 6-Ts	40	28.8	81.5
*Me 2-deoxy-α-D-galactopyranoside 6-Ts	ca. 21	53.1	91.6
Me 2-deoxy-β-D-galactopyranoside 6-Ts	40	28.9	56.7

Me = methyl Ts = tosylate

Apart from compound *, which was made in two ways (averages are of 8 values) each number is the average of 4 values reported in the Experimental, 5.

anhydro-ring formation does not take place easily, if at all.

For the above reasons boat conformations have been disregarded in the following discussion, but further evidence (e.g. the determination of the conformations of 3,6-anhydro-sugar derivatives by nuclear magnetic resonance spectroscopy) would obviously be of interest. This is especially so since it is claimed that certain reactions in the cyclohexane series proceed via boat conformations rather than via an alternative chair. For example, the reaction of trans-2-benzamido-trans-4-t-butylcyclohexyl methanesulphonate



with potassium acetate in ethanol to give a Δ^2-oxazoline is thought[21] to proceed via a boat form.

(b) Rate comparisons.

(i) In Table 2. are given the average first-order rate constants for cyclisation of the 6-tosylates. The footnotes to Table 9., given on p.83A, mention any peculiarities associated with the rate determinations. Table 3. contains rate constant ratios for certain pairs of compounds, for the purpose of comparison.

(ii) Before the rate constants are discussed in terms of conformational differences, it must be said that the observed differences in rate are not entirely due to stereochemical factors. According to the reaction scheme given earlier, the rate of cyclisation of the tosylates depends on the ionisation constant of the 3-hydroxyl group of the tosylate, as well as on the ease with which the

Table 3. Ratios of Rate Constants for Cyclisation of 6-Tosylates in 0.02N-Sodium Hydroxide.

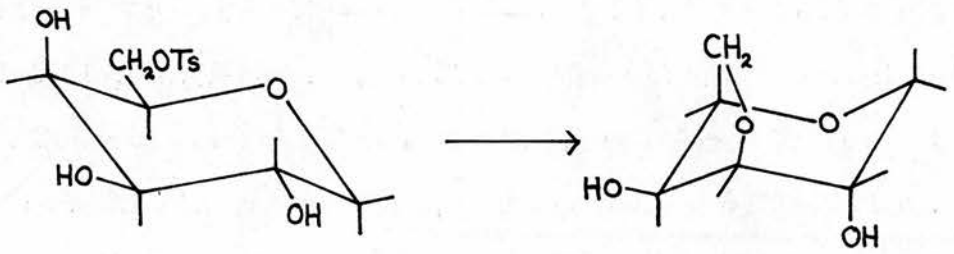
G = glucose	α = α-glycoside
Ga = galactose	β = β-glycoside
1 = 1-deoxy	2 = 2-deoxy

Galactose/glucose pairs	Water	50% Aqueous Dioxan
Gaα/Gα	8.5	7.9
Gaβ/Gβ	8.65	9.4
Ga1/G1	11.3	11.3
2-Deoxy-series.		
Ga2α/G2α	1.95	2.74
Ga2β/G2β	1.42	2.05
Ga12/G12	3.11	5.00
Anomeric pairs: α/β ratio		
Galactosides	1.48	0.96
Glucosides	1.50	1.14
2-Deoxy-galactosides	1.84	1.62
2-Deoxy-glucosides	1.34	1.21
1-deoxy/α-glycoside pairs		
Ga1/Gaα	13.6	15.5
G1/Gα	10.3	10.8
2-Deoxy-series.		
Ga12/Ga2α	2.96	4.07
G12/G2α	1.85	2.23
Effect of removing the hydroxyl at $C_{(2)}$ from:		
(a) 1-deoxy compounds		
Ga1/Ga12	3.70	3.24
G1/G12	1.02	1.44
(b) Glycosides		
Gaα/Ga2α	0.80	0.85
Gaβ/Ga2β	1.00	0.70
Gα/G2α	0.183	0.296
Gβ/G2β	0.163	0.314

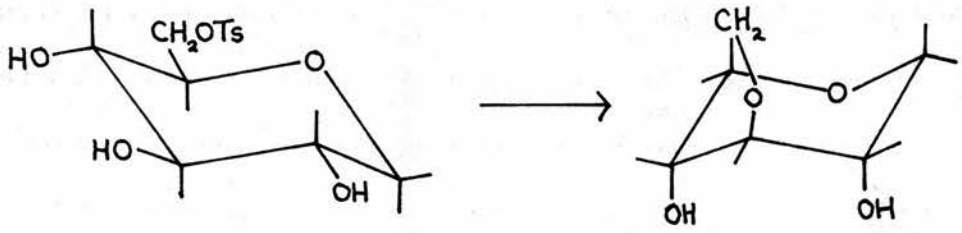
resulting ion undergoes cyclisation. In the present exposition it is assumed that this ionisation constant remains approximately constant in compounds of the same type, e.g. the tosylates of all the ordinary methyl glycosides. The differences in the ionisation constant of $OH_{(3)}$ which will be produced by removal of the hydroxyl group on $C_{(2)}$ or of the methoxyl group on $C_{(1)}$ are discussed later on.

(iii) Comparison between galactose and glucose isomers.

The first feature which is apparent from the results given in Tables 2. and 3. is that compounds in the galactose series react much faster than corresponding ones in the glucose series, the actual rate ratio in water being ca. 8.5 for the α- and β-glycosides and 11.4 for the 1,5-anhydro-D-hexitol 6-tosylates. (In aqueous dioxan the figures are similar). This finding is easily explained sterically, in the following way. Consider the case of the 6-tosylates of 1,5-anhydro-D-galactitol and - glucitol. In the galactitol case the product



1,5-3,6-dianhydro-D-galactitol



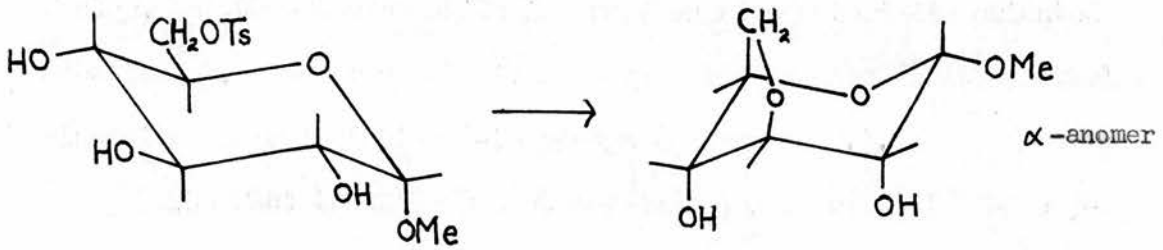
1,5:3,6-dianhydro-D-glucitol

possesses fewer non-bonded interactions than in the glucitol case, since the latter product contains two axial hydroxyls, while there is only one in 1,5 : 3,6-dianhydro-D-galactitol. On the other hand, in the tosylates in their normal conformation (C1) the total of non-bonded interactions is greater in the galactitol than in the glucitol. Since this means that the C1 ⇆ 1C conformational equilibrium is more to the right in the case of the galactitol, its rate of reaction will be greater. Hence it can be said that the presence of an axial substituent in the original 6-tosylate constitutes an accelerating factor, and that the opposite is true for an equatorially oriented substituent. The argument given above holds equally for the methyl glucoside and galactoside 6-tosylates. (See Table 3.).

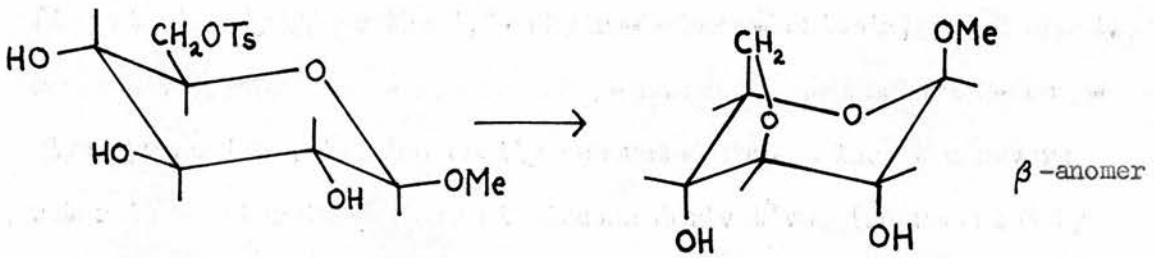
The fact that the galactose/glucose rate ratio in 2-deoxy-compounds is less than in the 2-hydroxy-series (see Table 3.), being (in water) only 3 for the 1,5-anhydro-2-deoxy-hexitols, and 2 and 1.4 respectively for the α-anomers and β-anomers of the methyl 2-deoxy-glycopyranosides, is also easily accounted for. Since the severe retarding factor in the normal glucose derivatives (represented by an $O_{(2)} - O_{(4)}$ diaxial interaction in the 1C-conformation) is absent from the 2-deoxy-derivatives, the latter compounds are expected to cyclise faster. In the galactose series there is no such great difference between the normal and the 2-deoxy-compounds, so that the galactose/glucose ratio is reduced.

(iv) Comparison between α- and β-anomers of glycosides. The next noteworthy aspect of the data is the value of the ratio of cyclisation rates for α- and β-anomers of glycoside 6-tosylates.

Table 3. shows this to be much smaller than the galactose/glucose ratio. Thus it is between 1.3 and 1.8 (in water) for all four α/β pairs examined. Steric arguments do not explain this low value; they predict, if anything, an even higher one than is observed for the galactose/glucose ratios, since in the 1C-conformation an axial group at $C_{(1)}$, such as occurs in the β-glycosides, is subjected to steric compression by two other axial groups, viz. $C_{(6)}$ and $O_{(3)}$, and not just one. Comparison of the formulae given below with those on p.13 illustrate the point.



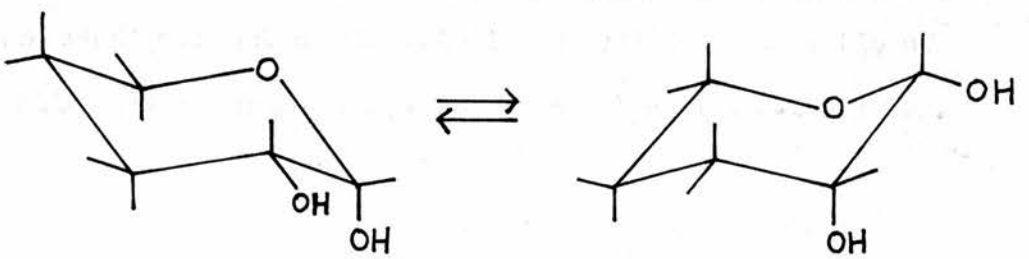
α-anomer



β-anomer

Two possible explanations of the low α/β rate ratio are (1) Passing interactions and (2) Dipole interactions.

(1) "Passing interaction" is the name given by Newth[4] to the steric interaction which might be expected to occur between adjacent cis-substituents on a 6-membered ring, during a change of conformation:-



In such a change, two cis groups must pass each other, and provided they are sufficiently bulky, the resulting steric hindrance will constitute an added barrier to the change. (See below, however). Newth[4] suggested passing interactions as an explanation for the facts that 1,6-anhydro-β-D-altrose 2-tosylate and 1,6-anhydro-β-D-altrose 3,4-ditosylate do not form epoxides on treatment with alkali (the 3-mono-tosylate does), and that methyl 4,6-O-benzylidene-α-D-glucoside 2-tosylate forms an epoxide much less easily than 1,5-anhydro-4,6-O-benzylidene-D-glucitol 2-tosylate. It may be noted, however, that these observations can also be explained in terms of electronic effects.

In regard to the present work, there are two points to be made. Firstly, since a passing interaction is a contribution to the energy barrier separating molecular conformations (here the Cl- and 1C-chair forms), it can only affect the rate of attainment of the conformational equilibrium, not its position. Hence it can only affect the rate of cyclisation if the conformational change is a rate-determining step. This is contrary to the assumptions usually made in the discussion of reactions which involve a change of conformation.[8,9b] Furthermore it may be noted that passing interactions cannot explain the low α/β rate ratio shown by the k_2 values derived by Baker, since from equation (1) given earlier, $k_2 = \underset{[OH^-]\to 0}{\text{Lim}} \; k_1/[OH^-]$, and since the conformational change cannot remain the rate-determining step at infinitesimal hydroxide concentrations.

Secondly, if passing interactions did have any effect on the reactivities of the derivatives dealt with here, certain differences

in behaviour would be observed between the normal sugars (having a hydroxyl group on $C_{(2)}$) and their 2-deoxy-analogues. Taking the example of anomeric glycosides and considering a possible 1,2-passing interaction, it is clear that such an interaction can occur only in the α-anomer of methyl D-gluco- or galacto-pyranoside 6-tosylates, since the two substituents concerned have to be cis. A 1,2-passing interaction would retard the cyclisation rate of the α-anomers with respect to the β-anomers. But in the corresponding 2-deoxy-glycosides, no 1,2-passing interaction can exist (hydrogen being too small), so that the α/β-anomeric rate ratio would be higher for the 2-deoxy-derivatives than for the normal sugars. In fact, it is lower (ca. 1.3) for the 2-deoxy-glucosides and higher (ca. 1.8) for the 2-deoxy-galactosides. It is therefore unlikely that appreciable 1,2-passing interactions exist in the "2-hydroxy"-glycoside derivatives described here.

(2) An alternative explanation for the observed low value of the α/β cyclisation rate ratio for anomeric 6-tosylates is the existence of important dipole interactions between the dipoles of the ring-oxygen atom, i.e. $O_{(5)}$, and the glycosidic oxygen, i.e. $O_{(1)}$.

Tentative calculations of the energies of interaction between these dipoles (see Appendix I) are promising. They indicate that the signs and magnitudes of the interactions will result in a disfavouring of conformations which have an equatorial glycosidic methoxyl group, i.e. β-glycosides in the Cl, unreactive, conformation, and α-glycosides in the 1C, reactive, conformation. On the other hand, for axial methoxyl groups, as in α-glycosides in the Cl- and β-glycosides in

the 1C-conformation, the dipole interactions are either zero or slightly favourable (see Appendix I). The net result will therefore be an increase in the energy difference in the $^{C1} \rightleftarrows {}^{1C}$ conformational equilibrium of α-anomers, and a decrease for the β-anomers. As explained earlier, this would lower the cyclisation rate for the former, and raise it for the latter, which would explain the unexpectedly low value of the α/β rate ratio.

The above ideas about dipole interactions are relevant to the problem of anomeric equilibria. In equilibration of the common methyl hexopyranosides with methanolic hydrogen chloride, the α-anomer usually predominates. This is not expected on steric grounds, since in the preferred conformation (C1) of the hexosides α-anomers have the methoxyl group axially oriented, so that in equilibrations the β-anomers (equatorial methoxyl, sterically favoured) shouldpredominate. The "anomalous" behaviour observed has been explained by Edward[22] in terms of electrostatic repulsions between the lone pairs of the ring-oxygen and the anomeric oxygen which destabilise the equatorial orientation. In an alternative approach, Lemieux[11,12] has postulated an "anomeric effect",[23a] consisting of an electrostatic attraction between the oxygen atom of an axially oriented (α) methoxyl group and a residual positive charge on $C_{(5)}$. A weakness common to both of these views is that they do not take account of the effect on the interactions concerned of the conformational orientation of the glycosidic methyl group with respect to rotation about the $C_{(1)}$- $O_{(1)}$ bond. (Hordvik[24] mentions this point). An approach along the lines suggested in Appendix I seems more satisfactory in this respect.

An interesting point now arises. If the assumption is correct that only the dipole interactions between $O_{(5)}$ and $O_{(1)}$ are important, then the absence of any or all of the other oxygen atoms of the sugar molecule should not affect its behaviour. In the cyclisation reactions of the present work this assumption appears to be substantiated, since the 2-deoxy-glycoside 6-tosylates have nearly the same α/β rate ratio (1.3, 1.8) as the normal glycoside 6-tosylates do (1.5). Data for anomerisation of the methyl 2-deoxy-D-galactopyranosides[25] also lend weight to the assumption, since again the α-anomer is preferred. (The ratio α-anomer/β-anomer at equilibrium is 2, if the optical rotation of the β-anomer in methanol is taken as $[\alpha]_D$ - 40°, the value found in the present work). Furthermore, the same results were obtained by Edward, Morand and Puskas[23a,b] for sugar analogues possessing only a ring-oxygen and a "glycosidic" oxygen. These authors found that in equilibration of 3-α- and β-methoxy-4-oxa-5α-cholestane with hydrogen chloride in methanol-tetrahydrofuran (1:1), the ratio of α-anomer to β-anomer at equilibrium was 3. Similar predominance of the α-anomer was found in equilibrations of the corresponding 3-isopropoxy, cyclohexyloxy, phenoxy and benzyloxy derivatives. In these steroids, ring A (the analogue of the pyranose ring) is fixed in what corresponds to the C1-conformation, so that the situation is in every way similar to that in the true sugars (apart, of course, from the absence of several oxygen functions).

It seems likely, in the light of these considerations, that any dipole interactions involving the 2-hydroxyl group in glycosides

can be neglected, although more comprehensive calculations of these interactions are desirable. (They would be very complicated, however, since both substituents can assume different rotational orientations). Also the "Δ-2 effect" of Reeves[1,26] would seem to be called in question to some extent by the above kinetic results.

Since the magnitude of any electrostatic interaction is inversely proportional to the dielectric constant of the medium concerned, the use of a less polar solvent should enhance any dipole effects. Aqueous dioxan (50% v/v), with a dielectric constant of 35[27] at 25°, was chosen as a suitable medium. The value for water at 25° is 78.

It would be expected that in the less polar solvent the α/β-anomeric rate ratio would be smaller, and in fact this was observed, the value for the methyl D-glucoside 6-tosylates being 1.1, compared with 1.5 in water, and for the methyl D-galactoside 6-tosylates 0.95, compared with 1.5 in water. In the 2-deoxy-glycosides the effect is less; for the 2-deoxy-glucoside 6-tosylates the α/β-ratio in aqueous dioxan is 1.2, compared with *ca.* 1.3 in water, and for the 2-deoxy-galactosides it is *ca.* 1.6 in aqueous dioxan, compared with *ca.* 1.8 in water. (See Table 3.).

(v) Comparison of 1-deoxy-compounds and α-glycosides. Another aspect of the data which is of interest in connection with the ideas described in the preceding section is the comparison of 1-deoxy-compounds (1,5-anhydro-D-hexitol 6-tosylates) with α-glycosides (methyl-α-D-glycoside 6-tosylates). The 1-deoxy-compounds cyclise much more rapidly than the α-glycosides, the ratio being 10.2 for the glucose

series and 13.6 for the galactose isomers, in water. The factors involved will now be considered in turn.

On steric grounds this result is not expected, since removal of the axial methoxyl group of the α-glycosides constitutes the removal of an accelerating factor (in the form of a reduction of the steric compressions suffered by the axial substituent, when the ring conformation changes from C1 to 1C). The results can be explained, however, by invoking the dipole interactions discussed in (iv). Since these favour the axial orientation of the methoxyl group, they would retard the cyclisations of the α-glycosides relative to those of the 1-deoxy-compounds.

Unfortunately, there are certain difficulties here. It would be expected that the 1-deoxy-compound / α-glycoside rate ratio would be considerably increased on changing the solvent to aqueous dioxan, but in fact the observed increase was very small, being from 10.2 to 10.8 in the glucose series, and from 13.6 to 15.5 in the galactose isomers (See Table 3.). In addition, it was found that the rate differences between the 1-deoxy-compounds and α-glycosides were much smaller when there was no hydroxyl group at $C_{(2)}$, in spite of the fact that the dipole factor should be equally important for the 2-deoxy-analogues. The observed ratio 1,2-dideoxy-compound / 2-deoxy-α-glycoside was 1.8 and 3 for the glucose series and galactose series respectively. Again there was a small increase on changing to aqueous dioxan. (See Table 3.).

An alternative explanation of the greater rate of cyclisation of the 1-deoxy-compounds compared with the α-glycosides is that the difference is due to an inductive electronic effect on $C_{(6)}$. It is thought that S_N2

reactions of tosyl esters have some S_N1 character[28], i.e. that the carbon atom attached to the tosyl group becomes slightly positive in the transition state. Hence the introduction of an electron-attracting methoxyl group at $C_{(1)}$ could lead to a decrease in the rate of reaction, because of a destabilisation of the transition state. However, this argument is not entirely convincing either, for two reasons. First, $C_{(6)}$ is rather remote from the $C_{(1)}$ - position, and second, the electronic retarding effect mentioned might be expected to be largely compensated by the accelerating effect of the glycosidic methoxyl group in increasing the ionisation constant of $OH_{(3)}$.

(vi) The effects of introducing a 2-hydroxyl group into certain of the compounds. It is interesting to compare the relative rates of the 1-deoxy-compounds and the 1,2-dideoxy-compounds (i.e. the 1,5-anhydro-2-deoxy-D-hexitol 6-tosylates). A consideration of the probable results of introduction of an equatorial hydroxyl group at carbon-2 of one of the latter leads to the following.

Firstly, the hydroxyl group is electron-attracting and will increase the acidity of the 3-hydroxyl group, thereby accelerating the reaction. On the other hand, the introduction at $C_{(2)}$ of an equatorial group, which will become axial during the conformational change and thereby encounter a serious 1,3-diaxial steric repulsion, will retard reaction. The fact that the cyclisation rates (in water) of the 6-tosylates of 1,5-anhydro-D-glucitol and its 2-deoxy-derivative are equal indicates that these opposing effects happen to cancel each other. However, in the galactose series it is clear that the steric

effect (retardation) of the 2-hydroxyl group must be less than in the glucose series. For in the latter the diaxial repulsion involved upon change of conformation of the ring is between two hydroxyl groups, $OH_{(2)}$ and $OH_{(4)}$, whereas in the galactose isomer the diaxial repulsion is between hydroxyl and hydrogen, and is therefore less severe. Consequently the steric factor in the galactose case should be outweighed by the electronic inductive effect, which is the same in both series, and so the cyclisation of the 1,2-dideoxy-galactose compound would be expected to be slower than that of the 1-deoxy-galactose derivative. In fact this was found to be the case, and the ratio 1-deoxy-galactose 6-tosylate / 1,2-dideoxy-galactose 6-tosylate was 3.7 (water).

It is interesting to compare the above with the effect of introducing a hydroxyl group at $C_{(2)}$ of the 2-deoxy-glycoside 6-tosylates. For both α- and β-2-deoxy-glucosides this reduced the rates to about one-fifth (in water) while for the 2-deoxy-galactosides there was little or no change. (See Table 3.). The balance of steric and electronic effects is therefore different here than for the 1-deoxy-compounds mentioned above, and the reason for this is not clear.

(vii) <u>The effect of solvent on the rates of cyclisation</u>. Some comment on the effect of change of solvent on the rates is necessary. The cyclisation of every compound was faster in aqueous dioxan than in water. This is expected, because of the fact that, in an S_N2 reaction involving a charged nucleophile, there is a spreading of electric charge in the transition state in the region of the three atoms directly concerned in the reaction (in the present case alkoxide ion at $C_{(3)}$,

$C_{(6)}$, and $O_{(6)}$), and this spreading will be facilitated by a fall in the dielectric constant of the solvent.[18b,29]

The data obtained here show that the factor of rate increase is almost the same in certain compounds of the same type, viz. 2.0 for the methyl α-glucoside 6-tosylate and 1.8 for the galactose isomer; 2.7 for the methyl β-glucoside ester and 2.8 for the β-galactoside; 2.1 for both 1,5-anhydro-hexitol esters. It will be noted that all these compounds possess a 2-hydroxyl group. In the 2-deoxy-series the amount of acceleration varies more. Thus the factor of rate increase is 1.2 for methyl 2-deoxy-α-glucoside 6-tosylate, but 1.7 for the 2-deoxy-α-galactoside; for the 2-deoxy-β-glucoside it is 1.35, while for the β-galactoside isomer it is 2.0. Even greater divergence is found in the 1,5-anhydro-2-deoxy-hexitol esters, the value being 1.5 for the "glucose" (arabino) isomer and 2.4 for the "galactose" (lyxo) isomer. These apparent discrepancies are so far not accounted for.

3. Reaction of 6-Tosylates in the Absence of Sodium Hydroxide.

Baker[17] and Mathewson[30] have found that aqueous solutions of 6-tosylates show a slow decrease in light absorption at wavelength 265 mμ, even in the absence of alkali. This is presumably the result of conversion of tosyl ester into tosylate ion. Although the compounds all reacted too slowly for accurate rate measurements to be made, it was found possible in the present work to obtain (spectrophotometrically) approximate rate constants for the more reactive tosylates, and the corresponding half-lives are given in Table.4. It was established that

all of the compounds (excepting the methyl 2-deoxy-β-galactoside tosylate) reacted at a rate less than 1% of the reaction rate of the corresponding tosylate in 0.02N-sodium hydroxide.

Table 4

6-Tosylate of:	Half-life at 22°
1,5-anhydro-2-deoxy-D-lyxo-hexitol	ca. 31 hr.
1,5-anhydro-D-galactitol	ca. 113 hr.
Me 2-deoxy-α-D-galactopyranoside	ca. 11.5 days.
Me 2-deoxy-β-D-galactopyranoside	ca. 36 hr.
Me α-D-galactopyranoside	ca. 30 days[30]
Me β-D-galactopyranoside	ca. 140 days[30]

Mathewson[30] obtained 3,6-anhydro-D-galactose dimethyl mercaptal by the action of ethanethiol and hydrochloric acid on an aqueous solution of methyl β-D-galactopyranoside 6-tosylate which had been heated at 50° for 8 days, and it therefore seems likely that the above reactions involve the formation of 3,6-anhydro-compounds by a neighbouring-group displacement of tosylate by the hydroxyl group on $C_{(3)}$.

Mathewson also found (by conductivity measurements) that methyl β-D-galactopyranoside 6-tosylate reacted considerably faster (ca. 4 times) than its α-anomer, and in the present work (see Table 4.) a similar relationship was demonstrated for the anomeric 2-deoxy-galactoside tosylates. This behaviour is remarkable, since in the reactions with sodium hydroxide the α-anomers were always more reactive. One possible explanation of the results is that for reactions in the absence of base, the diaxial repulsions between $O_{(3)}$ and $O_{(1)}$ in the 1C-conformation of β-

glycosides are less than in the reactions in alkali, because of the lesser solvation of the neutral hydroxyl group compared with that of the charged alkoxide group. (As explained earlier, these diaxial repulsions constitute a retarding factor for β-anomers). It was previously pointed out that the kinetic consequence of a change of configuration at $C_{(1)}$ involves a balance of steric and dipole factors, and it is reasonable to assume that the suggested decrease in steric interactions involving $O_{(3)}$ could lead to the observed reversal of the relative rates of cyclisation of anomers.

It was found that removal of the 2-hydroxyl group of galactoside or of 1,5-anhydro-galactitol 6-tosylates caused a considerable increase in rates of reaction (see Table 4.). This would be expected on steric grounds.

Mathewson found that the rates of reaction in water of the methyl glucoside 6-tosylates were too slow to allow the relative reactivities of the anomers to be compared, and in the present work, the rates for the 2-deoxy-glucoside derivatives turned out to be too slow for measurement by spectrophotometry.

It is clear that further work both on the products and rates of the reaction of 6-tosylates in water is desirable.

4. Conclusions, and Suggestions for Further Work.

Although the relative rates of cyclisation of the monosaccharide 6-tosylates show some features which are at present inexplicable, the general consistency of the rate ratios is encouraging. Although many of the observations can readily be explained (at least qualitatively) in conformational terms, the evidence obtained regarding the significance

of dipole interactions is of special interest.

A preliminary attempt has been made to interpret the observed rates in terms of the quantitative interaction energies derived by Angyal[10,31], but this has met with difficulties, and the quantitative aspects of interpretation of the results are therefore not discussed in detail here.

A continuation of the work described here, along the same lines, but supplemented by data for other 6-tosylates, is obviously required, and the following suggestions are made as the basis for further study.

(a) The 6-tosylates of methyl α- and β-D-mannopyranoside and of 1,5-anhydro-D-mannitol (all of which have hitherto been obtained as syrups) would be of interest.

(b) It would be of great interest to compare the behaviour of the 6-tosylates of 4-deoxy derivatives with that of the 2-deoxy compounds described here. However, the only known 4-deoxy-hexose with the right stereochemistry at $C_{(3)}$ is 4-deoxy-D-glucose[32].

(c) Useful information might be obtained by comparing the rates of cyclisation of the various compounds in a range of alkaline water-dioxan mixtures, e.g. proportions 1:2, 1:4 etc., in order to see whether the trends already observed are continued consistently as the dielectric constant of the solvent is reduced.

(d) A study of the cyclisation of 6-tosylates of anomeric C-glycosides[33], especially of those with large substituents on $C_{(1)}$, of thioglycosides, and of glycosides possessing bulky aglycones (e.g. the t-butyl group) would probably be rewarding.

B. PREPARATIVE ASPECTS

1. Comments on the Synthesis of 6-Tosylates

In the course of synthesis of monosaccharide 6-tosylates for the rate measurements which are the basis of PART I of the present work, a number of new compounds were prepared. All were obtained by tosylation with 1.1 mole of tosyl chloride. This method usually gives the 6-tosylates, which were confirmed as such by periodate oxidation. (See p.70 and Table 5.).

1,5-Anhydro-D-galactitol 6-tosylate (unusual for its slight solubility in all the usual organic solvents, excepting acetone) was made by tosylation of 1,5-anhydro-D-galactitol[34,35]. The tetra-acetate of the latter compound was obtained from acetobromo-D-galactose by a slight modification of the hydrogenolytic method of Zervas and Zioudrou [36], and was deacetylated by methanolic ammonia. The Zemplen method of deacetylation (transesterification using a catalytic amount of sodium methoxide in methanol) was unsuitable, owing to acidic by-products formed in the hydrogenolysis.

Tosylation of 1,5-anhydro-2-deoxy-D-lyxo-hexitol yielded 1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-tosylate, along with a ditosylate, which was not fully characterised.

The 6-tosylates were desired of all four methyl 2-deoxy-D-hexopyranosides having the 3-hydroxyl group on the same side of the ring as $C_{(6)}$, and this led to the development of new synthetic routes to these glycosides. One of the methods involved methoxymercuration,

and this part of the work is treated separately in PART II.

The known methyl 2-deoxy-β-D-glucopyranoside triacetate[37] was obtained from D-glucal triacetate by addition of hydrogen bromide[38], followed by reaction with methanol and silver carbonate; and also *via* methoxymercuration of the glycal (see p.108). The latter method is in fact more convenient, and gives a higher yield of methyl 2-deoxy-β-D-glucopyranoside triacetate. After deacetylation of this compound and tosylation of the resulting methyl 2-deoxy-β-D-glucopyranoside,[37,39] crystalline methyl 2-deoxy-β-D-glucopyranoside 6-tosylate was obtained.

Methyl 2-deoxy-α-D-glucopyranoside was prepared *via* methoxymercuration of D-glucal, as well as by treatment of 2-deoxy-D-glucose with methanolic hydrogen chloride. The overall yield from D-glucal is better by the former route.

The previously unknown methyl 2-deoxy-β-D-galactopyranoside triacetate was made in 10 - 15% yield by addition of hydrogen bromide to D-galactal triacetate[40], followed by reaction of the product with methanol and silver carbonate. Paper chromatography showed that the crude product consisted of approximately equal amounts of the methyl 2-deoxy-α-and -β-galactopyranoside acetates. The β-acetate could be separated from the mixture either by crystallisation, which was slow and inefficient, or by partition chromatography on silica gel, using dimethyl sulphoxide as stationary phase.[41] The latter method gave a better yield (15%). Deacetylation of the acetate gave crystalline methyl 2-deoxy-β-D-galactopyranoside, (previously known only as a syrup[25,42]) which

was also obtained by treatment of D-galactal with methanolic hydrogen chloride[43]; removal of the bulk of the methyl 2-deoxy-α-D-galactopyranoside by crystallisation, and chromatography of the mother-liquors on a cellulose column (yield ca. 3% by this route). The structure of the glycoside was confirmed by showing that 1 mole of periodate was consumed during oxidation with sodium periodate, and that in this process no formaldehyde was produced.[44] Tosylation of the glycoside gave methyl 2-deoxy-β-D-galactopyranoside 6-tosylate. The yield in this stage was unexpectedly low (ca. 35%).

Difficulties were experienced with methyl 2-deoxy-α-D-galactopyranoside 6-tosylate, which was prepared by two methods. The compound is reported to be a syrup by Foster, Overend, Stacey and Vaughan.[45] It was obtained first by the method of these authors by tosylation of methyl 2-deoxy-α-D-galactopyranoside, and could not be crystallised, even after chromatography of the crude product on silica gel.

An attempt was made to characterise the material by reaction with acetone and zinc chloride, in the hope of obtaining the known methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-tosylate.[46] This gave only syrup, which apparently was incompletely substituted (appreciable hydroxyl absorption in the infrared spectrum).

However, the above isopropylidene derivative was obtained by the method of Foster, Overend and Stacey[46] by tosylation of methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside[46,47] (see below). Removal of the isopropylidene group by treatment

with dilute methanolic hydrogen chloride provided the second route to methyl 2-deoxy-α-D-galactopyranoside 6-tosylate, which was again obtained as a syrup (but slightly impure).

Thin-layer chromatography (silica) using two solvent systems (see Experimental p.51) showed that the product of hydrolysis comprised three substances, viz, methyl 2-deoxy-α-D-galactopyranoside 6-tosylate (R_F 0.45), along with a little of the original isopropylidene compound (R_F 0.80) and a very small amount of material with R_F 0.55. The latter may be 2-deoxy-6-O-tosyl-D-galactose dimethyl acetal. Despite these impurities, the syrupy tosylates obtained by the two methods had similar optical rotations, travelled at the same rate on thin-layer chromatograms, and cyclised at the same rate with sodium hydroxide (see Experimental 5, Table 5). In each case the product of reaction with alkali was practically unaffected by periodate. The product of the acid hydrolysis rapidly consumed ca. 1.1 mole of periodate. The rather high value could be explained by over-oxidation, or by the presence of the above-mentioned acetal, which would consume two moles of periodate. The product is therefore methyl 2-deoxy-α-D-galactopyranoside 6-tosylate. The specimen of the 2-deoxy-α-galactoside 6-tosylate prepared by direct tosylation of the glycoside consumed only 0.7 moles of periodate, after oxidation for 2 and for 3 hours.

An interesting complication was encountered in the isopropylidenation[46,47] of methyl 2-deoxy-α-D-galactopyranoside. This reaction gave four substances, as shown by paper chromatography

(see Experimental p.49). The major constituents were the fastest-travelling (R_F 0.58), and a derivative with R_F 0.46 present in slightly smaller amount. Tosylation of the crude mixture increased the number of constituents to ten, but once more the largest spot on chromatograms (R_F ca. 0.75 on paper and on thin-layer) was the quickest moving, while the second-largest had R_F 0.4 - 0.5 (on paper) and 0.55 - 0.65 (on thin-layer). The crude syrup yielded crystals (A, 22%) with m. p. 92.5 - 94°, $[\alpha]_D^{18}$ +39° (c 1.8 in acetone). In paper chromatography this material travelled with R_F 0.66, and contained a little of the slower-moving substance (R_F 0.44). The authors mentioned previously[46] report as methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-tosylate a substance with m. p. 92 - 93° and $[\alpha]_D^{20}$ +44° (c 0.9 in acetone), but they did not confirm its structure. The mother-liquor of A gave crystals (B) in greater yield (32%). These had m. p. 82 - 85° (softened at 81°) and $[\alpha]_D^{18}$ +71° (c 1.9 in acetone). A paper chromatogram showed that the bulk of B was the slower-moving compound (R_F 0.45), but that a large proportion of the faster material (A, R_F 0.68) was present.

Since neither of the crude fractions A and B could be purified by recrystallisations, fraction A was chromatographed on a column of silica gel. The homogeneous material thus obtained had m. p. 94 - 95.5° and $[\alpha]_D^{20}$ +33° (c 2 in acetone). This was proved to be methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-tosylate by the fact that mild acid hydrolysis gave methyl 2-deoxy-α-

D-galactopyranoside 6-tosylate, characterised as above. The second tosylate was not further investigated, but it is probably methyl 2-deoxy-4,6-O-isopropylidene-α-D-galactopyranoside 3-tosylate, formed from methyl 2-deoxy-4,6-O-isopylidene-α-D-galactopyranoside present in the crude isopropylidenation product. Although condensation of acetone with sugars usually gives cyclic ketals with a 5-membered ring, a 6-membered ring may be obtained; for example Jones[48] prepared methyl 4,6-O-isopropylidene-α-D-glucopyranoside.

Tosylation of 1,2-O-ethylene-β-D-glucopyranose gave 1,2-O-ethylene-β-D-glucopyranose 6-tosylate. The former was made by the method of Helferich and Werner,[49] namely by simultaneous hydrolysis and cyclisation of 2-chloroethyl β-D-glucopyranoside tetra-acetate, using sodium hydroxide. (Difficulty was experienced in separating the product from the large quantity of sodium acetate produced. This could have been avoided by carrying out the deacetylation by the Zemplen method prior to the cyclisation, a sequence already described by Helferich and Werner[50]).

Note The m. p. of some of the tosylates was affected by the presence or absence of pyridine. It is difficult to remove the last traces of this solvent, and it was found that the m. p. of some compounds fell on recrystallisation, only to be raised again, when pyridine was added to the solvent being used. No doubt the explanation of this phenomenon is that in the presence of pyridine, minute amounts of acidic impurities or decomposition

products are prevented from causing early decomposition during heating. Even so, all the tosylates, (except for those of 1,5-anhydro-2-deoxy-D-lyxo-hexitol and methyl 2-deoxy-β-D-galactopyranoside), decomposed during melting, or immediately afterwards, and one or two had a higher m. p. when heated rapidly than with slow heating.

2. Reaction of 1,2-O-Ethylene-β-D-glucopyranose 6-Tosylate with Sodium Methoxide.

The above reaction was investigated for reasons discussed earlier (p. 11). Under mild conditions (3-fold excess of 0.5 N-sodium methoxide in methanol for 25 hr. at room temperature, followed by 2 hr. at 40°), ca. 80% of the tosylate was recovered, and no other products were isolated.

With vigorous treatment (12-fold excess of 0.9 N-sodium methoxide solution, refluxing for 48 hr., followed by 3 days at room temperature), all the tosylate appeared to react and sodium tosylate was isolated. The remainder of the product was a mixture (partly crystalline, partly syrupy), which requires further investigation. Chromatographic evidence indicated the presence of 1,2-O-ethylene-β-D-glucopyranose in both the solid and the syrupy portions of the mixture, and it is clear that, even though some of the 3,6-anhydro-derivative may be produced, a number of side reactions are occurring.

The above results suggest that formation of a 3, 6-anhydro-ring via a boat transition state is very slow.

3. Methods Used in Sodium Periodate Oxidations

The usual and the most accurate method of determining uptake of periodate is to liberate iodine from the unreacted periodate ion by means of iodide ion, the solution being buffered to pH 6-7. The iodine is then titrated with sodium arsenite.[51] However, R. Baker found that oxidation of 1,5-anhydro-2-deoxy-D-arabino-hexitol and its 6-tosylate gave products which, in neutral solution, reduce iodine to iodide, so that the above method was useless in these cases.[52] In acid solution this reduction does not take place, which allows an alternative method to be used, viz. liberation of iodine by means of iodide in ca. 0.1N-sulphuric acid, and titration of the iodine with sodium thiosulphate. The disadvantage of this method is that in these conditions iodine is liberated not only from the unreacted periodate, but also from the iodate produced during oxidation of the organic compound. As a result the accuracy obtainable is less. This alternative method was used in the present work for structure confirmations, since a number of 2-deoxy compounds[53] were involved.

In the investigation of the completeness of cyclisation of the tosylates with caustic soda (see below) the "neutral" method was thought to be suitable, since none of the 3,6-anhydro-compounds expected to be formed would be affected by periodate.

4. Products of Reaction of 6-Tosylates with Alkali

Previous work by R. Baker[17] has confirmed that the sole product of cyclisation (in dilute aqueous alkali) of the known

6-tosylates mentioned in the present discussion is the corresponding 3,6-anhydro-compound. The evidence for this was the isolation of the latter and non-oxidation of the final reaction mixture by sodium periodate. For various reasons preparation of the 3,6-anhydro-derivatives of the four new monocyclic tosylates (see p. 28) has not been carried out. The only one known is 1,5:3,6-dianhydro-D-galactitol.[35]

However, control runs, carried out in the same conditions as the kinetic experiments, gave final solutions which were practically unaffected by sodium periodate. (See p. 72 and Table 6). This suggests that the 3,6-anhydro-compounds are in fact the sole products, since the glycosides which might have been formed if detosylation had occurred without cyclisation would have consumed periodate.

EXPERIMENTAL

1. General Information on Experimental Procedures

(a) Evaporations were carried out under reduced pressure at 40° or below, usually on a rotary evaporator. Optical rotations were measured in 1 dm. tubes (5 ml. or 10 ml.) and infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord spectrophotometer. The methanol used in deacetylations and methoxymercurations was dried according to Vogel.[54a] The light petroleum used had b. p. 60 - 80°. Solutions were deionised by stirring with portions of Amberlite ion-exchange resins (IRA-400 for anions, IRC-50 for cations), or by passage of the solution through a column of the appropriate resin.

(b) Paper chromatography (descending) was done on Whatman No. 1 paper, using the following solvent systems:

(i) n-butanol-ethanol-water (4:1:5, upper layer),

(ii) dimethyl sulphoxide as stationary phase and di-isopropyl ether as mobile phase. The procedure of Wickberg[55] was used, except that after application of the dimethyl sulphoxide as a solution (25%) in toluene, the papers were heated at ca. 80% for 1 min., instead of at 60°. At the lower temperature the solvent front tended to be slow-moving and uneven, and the spots of applied compounds spread out to a large size. When dimethyl sulphoxide was used as stationary phase, the papers were heated at 120° for 10 min. before being sprayed.

(iii) dimethyl sulphoxide as stationary phase and di-isopropyl ether-benzene (1:1) as mobile phase.

(iiia) dimethyl sulphoxide as stationary phase and di-isopropyl ether-benzene-dimethyl sulphoxide (5:5:1) as mobile phase. This system was used only with 6-tosylates, but was less satisfactory than system (iv), owing to lack of reproducibility of R_F-values, even on the same chromatogram.

(iv) propane-1,2-diol-water (4:1) as stationary phase and benzene-chloroform (1:1) as mobile phase. The procedure used here was that of Bolliger and Meyer.[56] This system was the most suitable for tosylates. Owing to the slow rate of travel of these compounds with the system, R_F-values were usually not obtained. Instead the rate (R_{MT}) relative to that of methyl α-D-mannopyranoside 3-tosylate was used as a measure of comparison between compounds.

Sprays used were:

(a) a mixture of 4 parts of 2% aqueous sodium periodate solution with 1 part of a solution (1%) of potassium permanganate in aqueous sodium carbonate (2%).[57] This is a generally useful spray, which, however, attacks the paper after 30 - 50 min.

(b) aqueous sodium periodate (2%), followed by a solution (1%) of p-nitroaniline in ethanolic hydrogen chloride (20% V/V).[58] This spray is specific for 2-deoxy derivatives, including glycals, and is very sensitive. Yellow or orange spots appear, which give a strong yellow fluorescence, when viewed in ultraviolet light.

(c) 0.1N-sodium hydroxide in 50% aqueous ethanol, followed after 15 min. by treatment (b). This spray had the same specificity as (b), but was suitable for acetyl esters.

(d) a solution (0.04%) of Rhodamine G[59] in ethanol, preceded by two immersions of the paper in a saturated solution of iodine in light petroleum. This spray was suitable for sugar mercurials.

(e) a solution (1%) of diphenylamine in ethanol.[60] This spray was very sensitive for tosylates, which showed up as light-blue fluorescent spots in ultraviolet light, after irradiation for a few seconds.

(f) a solution (0.001%) of phenol red indicator in aqueous 0.01N-sodium hydroxide. This spray was suitable for tosylates, which appeared as yellow spots (not permanent) on a red background but was less sensitive than (e).

(g) a solution (2%) of aniline sulphate in 50% aqueous ethanol. This spray is suitable for 3,6-anhydro-compounds, in addition to glycosides and free sugars. Heating is required (usually for 1 hr. at *ca.* 130°.)

(h) a solution (0.2%) of 2,4-dinitrophenylhydrazine in aqueous 2-N-hydrochloric acid. Cf. Vogel.[54b] This spray is specific for isopropylidene-compounds, orange-red spots being produced immediately on spraying. Heating at *ca.* 90° (cautiously, to prevent disintegration of the paper) changed these to brown.

(j) an ethanolic solution of 0.5N-sodium hydroxide, preceded by passage of the paper through a dilute solution of silver nitrate in acetone containing the minimum of water. After a suitable time the paper was immersed briefly in aqueous 6 N-ammonium hydroxide solution.

This spray[61] was generally applicable, but did not detect 2-deoxy-glycosides.

Thin-layer chromatography[62] (ascending) was done on glass plates (20 x 5 cm.), coated with Merck silica gel G by means of a Desaga spreader. The silica was highly activated by heating the plates at 120° for 1 hr. The solvent front was allowed to travel 10 cm. beyond the starting-line.

Solvent systems used were:

(v) benzene-ether (1:1)

(vi) ethyl acetate

(vii) water as stationary phase (applied by spraying lightly and allowing to dry in air) and solvent (i) (butanol-ethanol-water, 4:1:5) as mobile phase. This system was used for substances which normally would be chromatographed on paper, using solvent (i), but which could not easily be shown up without attack of the paper by the spray reagents required. It gave as efficient separation as did paper, and had the advantage of rapid solvent flow (ca. 3 hr. for 10 cm. travel).

Sprays used were: (a), (e) and (g) (see above).

(c) It was found to be convenient to remove di- or tri-tosylates from methyl 2-deoxy- α-D-galactopyranoside 6-tosylate by adsorption chromatography on silica. Methyl 2-deoxy-3,4-O-isopropylidene- α-D-galactopyranoside 6-tosylate was also easily purified in this way.

Columns 18 - 20 cm. long, diameter 1.7 - 2.5 cm., were prepared

by slurrying silica gel (Hopkins and Williams' "M.F.C." grade) in an appropriate solvent, pouring the suspension into the glass column, and allowing it to settle. The progress of the elution was followed by spotting each fraction of the effluent on paper impregnated with spray (e), the presence of tosylate being shown by the appearance of a fluorescent spot upon illumination with ultraviolet light. The identity and purity of the material in the various fractions were obtained by thin-layer chromatography of these on silica gel, using solvent (v) or (vi) and spray (e). The volume of fractions was 10 - 15 ml.

(d) Tosylations were carried out as follows, unless otherwise stated. A solution of the carbohydrate (10% or less, depending on solubility) in AnalaR pyridine (dried by distillation from barium oxide) was cooled to between 0° and -10° and then rapidly stirred, with the exclusion of moisture, while a solution (10 - 20%) of tosyl chloride (1.05 or 1.10 moles) in the pyridine was added dropwise during a period of 20 min. to 1 hr. The solution was then stirred at 0° or below for a short time, after which the well-stoppered flask was left in the cooling bath overnight (17 - 24 hr.) to reach room temperature. (For tosylations of 0.2 g. of material or less, the reaction was done in a 10 ml. Quickfit flask, the solution of tosyl chloride being added dropwise during 5 - 7 min. from a pipette (2 ml.) fitted tightly into the mouth of the flask by a perforated cork. During the addition the flask was swirled and cooled in the ice-salt bath). The mixture was then cooled to

below 5° and water (10 - 20 moles) was added dropwise, with stirring, to decompose excess tosyl chloride. After at least an hour at room temperature the pyridine was removed by repeated (2 - 6 times) evaporation in the presence of ethanol, followed by dissolution in chloroform and washing of the solution with 0.2 - 0.5N-sulphuric acid solution. Since some of the tosylates are appreciably water-soluble, this operation was kept to a minimum (2 - 4 times) and was sometimes omitted. Before being dried with anhydrous sodium sulphate or magnesium sulphate (usually in the presence of a little solid sodium bicarbonate) the chloroform solution was washed with saturated aqueous sodium bicarbonate solution.

2. Preparation of Monosaccharide 6-Tosylates

(a) 1,5-Anhydro-D-galactitol 6-tosylate

1,5-anhydro-D-galactitol[34-36] Acetobromo-D-galactose (41 g., 0.1 mole, m. p. 74 - 78°) made by the method of Barczai-Martos and Körösy[63] was dissolved in ethyl acetate (350 ml.) containing triethylamine (0.1 mole) and hydrogenated according to the method of Zervas and Zioudrou,[36] except that Raney nickel (46 g.) was used in place of palladised charcoal. The uptake of hydrogen (at 18° and 750 mm. pressure) after 125 hr. was 1800 ml. or 75% of the theoretical amount. After the catalyst had been removed by filtration, the solution was washed twice with water to remove triethylamine, dried (magnesium sulphate) and evaporated to dryness. The crude, solid 1,5-anhydro-D-galactitol tetra-acetate was dissolved in methanol (300 ml.) and deacetylated by addition of a solution of anhydrous

ammonia in methanol[64,65] (300 ml., saturated at 0°), followed by storage in the refrigerator for 21 hr. Since neither evaporation to dryness nor repeated extraction of the solid with boiling chloroform removed all the acetamide, it was destroyed by heating the solid product in N-sodium hydroxide solution (75 ml.) at 55° for 1 hr. After the sodium ions had been removed by passage of the resulting solution through IRC-50 cation-exchange resin, the product was crystallised by evaporating to dryness and warming the resulting syrup with ethanol. The solid obtained (6.2 g., m. p. 110 - 111°) was recrystallised from ethanol (50 ml.) to give pale-brown needles (5.0 g.) with m. p. 112 - 113-5° and $[\alpha]_D^{19}$ +78° (c 0.9 in H_2O). The mother liquor yielded white crystals (0.40 g.) with m. p. 112.5 - 113° and $[\alpha]_D^{19}$ +80° (c 0.6 in H_2O). Fletcher and Hudson give m. p. 114 - 115° and $[\alpha]_D$ + 76.7° (c 1.1 in H_2O),[34] and m. p. 113 - 114°, $[\alpha]_D^{20}$ +78° (c 0.8 in H_2O).[35] All the material obtained was shown to be pure by paper chromatography using solvent (i) and spray (j). It travelled as a single spot (R_F ca. 0.21). Yield 33%.

Tosylation Using the method described above 1,5-anhydro-D-galactitol (4.10 g., 25 mmoles) dissolved in pyridine (50 ml., not dried) was treated with tosyl chloride (5.25 g., 27.5 mmoles). During working-up the product crystallised, when ethanol was added to the syrup obtained after evaporation of the pyridine. The shiny plates produced (A, 2.87 g.) had m. p. 137° and $[\alpha]_D$ +42° (c 0.3 in C_5H_5N). The mother-liquor was repeatedly evaporated with ethanol and the

resulting syrup dissolved in chloroform (40 ml.). When the solution obtained was washed with water, crystallisation occurred, and filtration of the two liquid layers gave crystals (B, 1.3 g.) with m. p. 137 - 138° (decomp.). Attempts to obtain further solid from the mother-liquor were unsuccessful. Yield 52%. Recrystallisation of A and B (combined) from methanol (100 ml.) gave plates (1.60 g., m. p. 142 - 143° on slow heating, 151 - 152° on rapid heating, both values being unchanged by a second recrystallisation from methanol) which had $[\alpha]_D^{17}$ +41° (c 0.7 in C_5H_5N) (Found: C, 49.4; H, 5.9; S, 9.7. $C_{13}H_{18}O_7S$ requires C, 49.1; H, 5.7; S, 10.0%). The mother-liquor yielded shiny plates (0.32 g.) with m. p. 142 - 144° (slow heating) and 149 - 151° (rapid heating). In every case the compound gave a brown melt. The 1,5-anhydro-D-galactitol 6-tosylate so obtained travelled as one spot (R_{MT} ca. 0.35) in paper chromatography, using system (iv) and spray (f), and in thin-layer chromatography (R_F ca. 0.1), using solvent (vi) and spray (e).

(b) 1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-tosylate and 1,5-anhydro-2-deoxy-D-lyxo-hexitol ditosylate

D-galactal [25,46,64,66-70]

Using the procedure of Helferich, Mulcahy and Ziegler,[67] and Kuhn and Baer,[68] (slightly modified by starting with solid acetobromo-D-galactose instead of making it in situ), D-galactal triacetate was prepared as a syrup. Since this could not be distilled without partial decomposition* and evolution of acetic acid, even at 175-190°

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* It was later found that the crude product could be distilled without decomposition, by using an annular still at 150 - 170° (bath)/0.3 mm.

(bath)/0.002 mm., the acetate was not purified, but was deacetylated with sodium methoxide in methanol. The pale yellow solid so obtained was extracted (4 times) with boiling ethyl acetate, and the extracts yielded crystalline D-galactal. In a typical preparation the yield of galactal [11.4 g., m. p. 94 - 104°, $[\alpha]_D^{17}$ -20° (c 1 in MeOH)] from the acetobromo-sugar (76 g., m.p. 74 - 78°) was 42%. The material (R_F ca. 0.47) was shown by paper chromatography with solvent (i) and spray (j) to contain small amounts of D-galactose (R_F 0.13) and 1,5-anhydro-D-galactitol (R_F 0.22). The physical constants of D-galactal reported in the literature vary widely: Tamm and Reichstein[69] give m. p. 90 - 92°, Montigel[70] gives m. p. 108 - 112°; Foster, Overend and Stacey[46] quote $[\alpha]_D^{20}$ -29° (c 2 in MeOH), while Overend, Shafizadeh and Stacey[25] report $[\alpha]_D^{18}$ +5° (c 1.2 in MeOH). 1,5-anhydro-2-deoxy-D-lyxo-hexitol[25] was obtained by the method of Overend, Shafizadeh and Stacey[25]. D-galactal [5.0 g., m. p. 94 - 104°, $[\alpha]_D^{17}$ -20° (c 1 in MeOH)] was hydrogenated at atmospheric pressure in methanol (200 ml.) in the presence of Raney nickel catalyst (5 g.) for 4 hr., the final uptake of hydrogen being 91% of the theoretical amount. The product was obtained by crystallisation from ethanol as elongated prisms (2.67 g.) with m. p. 126.5 - 128° and $[\alpha]_D^{16}$ +48° (c. 0.4 in H_2O). The mother-liquors yielded further material (1.14 g., m. p. 125 - 127°). Yield 75%. Paper chromatography of the compound (R_F 0.35) using solvent (i), spray (j) showed the presence of a little impurity (R_F 0.21), which was probably 1,5-anhydro-D-galactitol (R_F 0.21).

The authors mentioned[25] give m. p. 128 - 129°, $[\alpha]_D^{20}$ +42° (c 0.5 in H_2O).

Tosylation Using the method described earlier, 1,5-anhydro-2-deoxy-D-lyxo-hexitol (3.70 g., 25 mmoles), pyridine (45 ml., not dried) was esterified with tosyl chloride (5.25 g., 27.5 mmoles). The product was crystallised from chloroform-light petroleum as fine needles (2.13 g., 28%) with m. p. 105 - 105.5°. The mother-liquor yielded further material (0.11 g.) with some difficulty. Two recrystallisations from the same solvent gave 1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-tosylate (1,42 g.) with m. p. 109 - 110° (no decomp.) and $[\alpha]_D^{17}$ +15° (c 1 in $CHCl_3$), these constants being unaltered on a third recrystallisation. (With rapid heating the m. p. was 113 - 114°, no decomp.) (Found: C, 51.7; H, 5.8; S, 10.2. $C_{13}H_{18}O_6S$ requires C, 51.7; H, 6.0; S, 10.6%. The compound travelled as one spot on thin-layer chromatograms [R_F 0.39, solvent (vi) and spray (e)] and on paper [R_{MT} 2.1, system (iv) and spray (f)].

Attempts to obtain more mono-tosylate from the combined mother-liquors were unsuccessful, but after evaporation to dryness, dissolution in chloroform, and washing with aqueous cadmium chloride solution (5%) to remove traces of pyridine, crystallisation from ethanol-light petroleum gave white prisms (0.69 g., 6%) with m. p. 117 - 119°, $[\alpha]_D^{17}$ +47° (c 0.6 in $CHCl_3$). Recrystallisation from chloroform-light petroleum produced prisms of a 1,5-anhydro-2-deoxy-D-lyxo-hexitol ditosylate with m. p. 121 - 122°, unchanged on

recrystallisation from the same solvents (Found: C, 52.6; H, 5.4; S, 13.9. $C_{20}H_{24}O_8S_2$ requires C, 52.6; H, 5.3; S, 14.0%).

(c) Methyl 2-deoxy-α-D-galactopyranoside 6-tosylate[45] was made in two ways.

(i) From methyl 2-deoxy-α-D-galactopyranoside,[25,43,46,66a,69,71] which was obtained from D-galactal (14 g.) by the action of 0.2% methanolic hydrogen chloride (150 ml.) according to the method of Overend, Shafizadeh and Stacey.[25] Crystallisation from ethyl acetate gave the glycoside as elongated prisms (6.23 g., 51%) with m. p. 111 - 113° and $[\alpha]_D^{20}$ +174° (c 1 in MeOH). These constants agree with the literature values,[25,66a] and the compound showed infrared absorption at $\nu_{max.}$ 830 (m) and 870 (w) $cm.^{-1}$ (Nujolmull). Barker, Bourne, Stephens and Whiffen[72] report $\nu_{max.}$ 817 (s) and 868 (m) $cm.^{-1}$ Paper chromatography of the compound (R_F 0.48) with solvent (i) and spray (b) showed it to contain very small amounts of 2-deoxy-D-galactose (R_F 0.26) and D-galactose (R_F 0.15), which were not completely removed by recrystallisation of a portion (3.0 g.) of the product from ethyl acetate-ethanol (12:1, 30 ml.). The material thus obtained had m. p. 112 - 114.5°.

The mother-liquor of the original product yielded sticky crystals (2.2 g.) with $[\alpha]_D$ +117° (c 0.5 in MeOH), which turned yellow after 2 weeks and were rejected. The remaining mixture gave a syrup (A, 7.4 g.) with $[\alpha]_D^{23}$ +50° (c 1 in MeOH), from which the 2-deoxy-β-glycoside was obtained by chromatography, as described later.

Tosylation. Using the method given earlier, methyl 2-deoxy-α-D-galactopyranoside (0.50 g., 2.81 mmoles) in pyridine (10 ml.) was treated with tosyl chloride (0.56 g., 2.94 mmoles) in pyridine (10 ml.). The bulk of the pyridine was removed by repeated evaporation with ethanol and the last traces were removed by washing the chloroform solution of the resulting syrup with aqueous cadmium chloride solution (5%). The syrupy product was purified by chromatography on silica gel, as described earlier. The eluant was ether (dried with sodium) and 20 fractions (15 ml.) were collected. Methyl 2-deoxy-α-D-galactopyranoside 6-tosylate was obtained from fractions 9 - 14 as a colourless syrup (0.50 g., 54%), which had $[\alpha]_D^{18}$ +90° (c 1.7, $CHCl_3$) and travelled as one spot (R_F 0.4 - 0.5) in chromatography on paper, using system (iiia) and spray (e), and on silica (thin-layer, R_F ca. 0.5) using solvent (vi). Fractions 2 - 4 contained three tosylates, which travelled fast in thin-layer chromatography using solvent (v) (R_F 0.35, 0.43, and 0.70).

(ii) From methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-tosylate[46]

Methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside[46,47] was made by the method of Foster, Overend and Stacey[46] by shaking methyl 2-deoxy-α-D-galactopyranoside (2.79 g.) in acetone (50 ml.) with zinc chloride (5 g.) for 20 hr. in the presence of calcium sulphate (3 g.) as drying agent. Working up was by addition of the theoretical amount of potassium bicarbonate solution (50 ml.), filtration and washing of the residue with acetone (60 ml.). Concentration to 50 ml. and

extraction with 4 x 25 ml. of chloroform gave a syrupy product (3.5 g.), which had $[\alpha]_D^{18}$ +79° (c 2 in acetone) and showed very sharp hydroxyl absorption in the infrared. The syrup consisted mainly of two substances, as shown by paper chromatography, using system (ii) and spray (h). The major component (R_F 0.58) was the faster-moving, while the minor one had R_F 0.46. The two other constituents were only traces.

Tosylation. The product (3.38 g., 15.5 mmoles) in pyridine (20 ml.) was treated with tosyl chloride (3.28 g., 17.2 mmoles) in pyridine (15 ml.), using the method described earlier. After 19 hr. water was added to decompose the excess of tosyl chloride. After removal of the pyridine by evaporation, dissolution of the resulting syrup in chloroform (50 ml.), washing of the solution with sodium bicarbonate, drying, and decolourisation with charcoal, a syrup was obtained, which crystallised with difficulty in the presence of a little chloroform. Chromatography of the crude product on paper using system (ii) and spray (e) showed ten tosylate constituents. The largest spot had R_F 0.73 and the next largest had R_F 0.55. Crystallisation from ethanol-light petroleum (2:1, 30 ml.) gave fine needles (A, 1.26 g., 22%) with m. p. 92.5 - 94° and $[\alpha]_D^{18}$ +39° (c in 1.8 in acetone). Evaporation of the nother-liquor of A gave a solid mass, which was recrystallised from ethanol-light petroleum (1:3, 14 ml.) to give shiny prisms (B, 1.86 g., 32%) which had m. p. 82 - 85° (softened 81°) and $[\alpha]_D^{18}$ +71° (c 1.9 in acetone). Only syrup and sticky crystals could be

obtained from the mother-liquor of B. The infrared spectra of A and B differed markedly. Paper chromatography as above showed that A consisted of a substance travelling with R_F 0.66, contaminated with a small amount of material with R_F 0.44, while B appeared to be a mixture of the same two compounds, there being somewhat more of the slower-moving one than of the faster. Neither A or B could be purified by recrystallisations, and since A had constants similar to those of the methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-tosylate reported by Foster, Overend and Stacey,[46] portion B was not further investigated. After two recrystallisations, first from ethanol-light petroleum (1:20) and then from acetone-light petroleum (1:30) the m. p. of A had risen to 93.5 - 94.5°, but paper chromatography showed that a little of the slower-moving material was still present.

A portion (0.5 g.) of the product thus obtained was purified by chromatography on a column of silica gel (35 g., 1.7 x 22 cm.), using benzene-ether (19:1) as eluent. (The ether was sodium-dried and the benzene was distilled AnalaR grade). The material was dissolved in the eluent (10 ml.), applied to the column and eluted with the solvent (300 ml.). In all 31 fractions (9 - 10 ml.) were collected. Spotting of these on paper sprayed with diphenylamine — spray (e) — showed that fractions 12 - 30 contained tosylate material. Thin-layer chromatography of these on silica, using solvent (v), showed that fractions 20, 23 and 26 contained only fast-moving tosylate (R_F 0.70), while 29 contained a trace of the slower material (R_F 0.60)

besides. Evaporation of fractions 12 - 27 (combined) gave methyl 2-deoxy-3,4-O-isopropylidene- α-D-galactopyranoside 6-tosylate (0.47 g., 94% recovery) as short needles, which were recrystallised from ethanol-light petroleum (1:17, 5.3 ml.) to give elongated prisms with m. p. 94 - 95.5° and $[\alpha]_D^{20}$ +33° (c 2 in acetone) (Found: C, 55.2; H, 6.6; S, 8.65. Calc. for $C_{17}H_{24}O_7S$: C, 54.8; H, 6.5; S, 8.6%).

De-isopropylidenation to give methyl 2-deoxy- α-D-galactopyranoside 6-tosylate. The isopropylidene-tosylate was found to be unaffected by 0.001N-methanolic hydrogen chloride at room temperature in the course of 30 min. The optical rotation of the compound in the solution was $[\alpha]_D^{18}$ +28° (c 1 in MeOH-HCl).

A repeat experiment was carried out at 19° using stronger acid. The compound (50 mg.) was dissolved in 0.05N-methanolic hydrogen chloride, using a volumetric flask. The optical rotation of the solution increased from +0.29°, 5 min after dissolution to +0.75°, 130 min. after dissolution. When the solution was neutralised with silver carbonate 40 min. later, the rotation had not changed further. Assuming complete conversion to methyl 2-deoxy- α-D-galactopyranoside 6-tosylate, the final optical rotation of the product was $[\alpha]_D^{19}$ +84° (c 0.89 in MeOH-HCl).

Thin-layer chromatography of the reaction solution [silica, solvent (vi), spray (e)] showed that the bulk of the product was the expected 6-tosylate (R_F ca. 0.45), while there was a little

unreacted isopropylidene-compound (R_F ca. 0.80), besides a trace of an unknown substance (R_F ca. 0.55). Chromatography, using heavy spotting of the starting material, confirmed that the unknown was absent from it, and that it must therefore have been produced by the action of the acid. Chromatography as above also showed that the impurity was not methyl 2-deoxy-β-D-galactopyranoside 6-tosylate, which could not be resolved from the α-anomer, but travelled more slowly than the impurity. The latter is possibly the 2-deoxy-α-D-galactofuranoside isomer, or else 2-deoxy-6-O-tosyl-D-galactose dimethyl acetal.

(d) Methyl 2-deoxy-β-D-galactopyranoside 6-tosylate

Methyl 2-deoxy-β-D-galactopyranoside[25,42] was made in two ways:- (i) by chromatography of syrup A mentioned in (c) above, (ii) from D-galactal triacetate.

(i) Using a column of powdered cellulose (56 x 3.2 cm., dry-packed tightly) syrup A was chromatographed in two equal portions by elution with n-butanol half-saturated with water. Prior tests of various solvent systems on paper showed that this mixture was the best eluant and gave almost complete separation of the anomers of methyl 2-deoxy-D-galactopyranoside (R_F-values ca. 0.40 and ca. 0.35, respectively, for the α- and β-anomers). The butanol used was "reagent grade", refluxed over potassium hydroxide and then distilled. The progress of the elution was followed by the convenient and sensitive method of spotting each of the fractions on paper, which was then sprayed with sprays (b). The fractions were collected

CHROMATOGRAPHY ON CELLULOSE OF THE RESIDUE A FROM THE ACTION OF METHANOLIC HCl ON D-GALACTAL

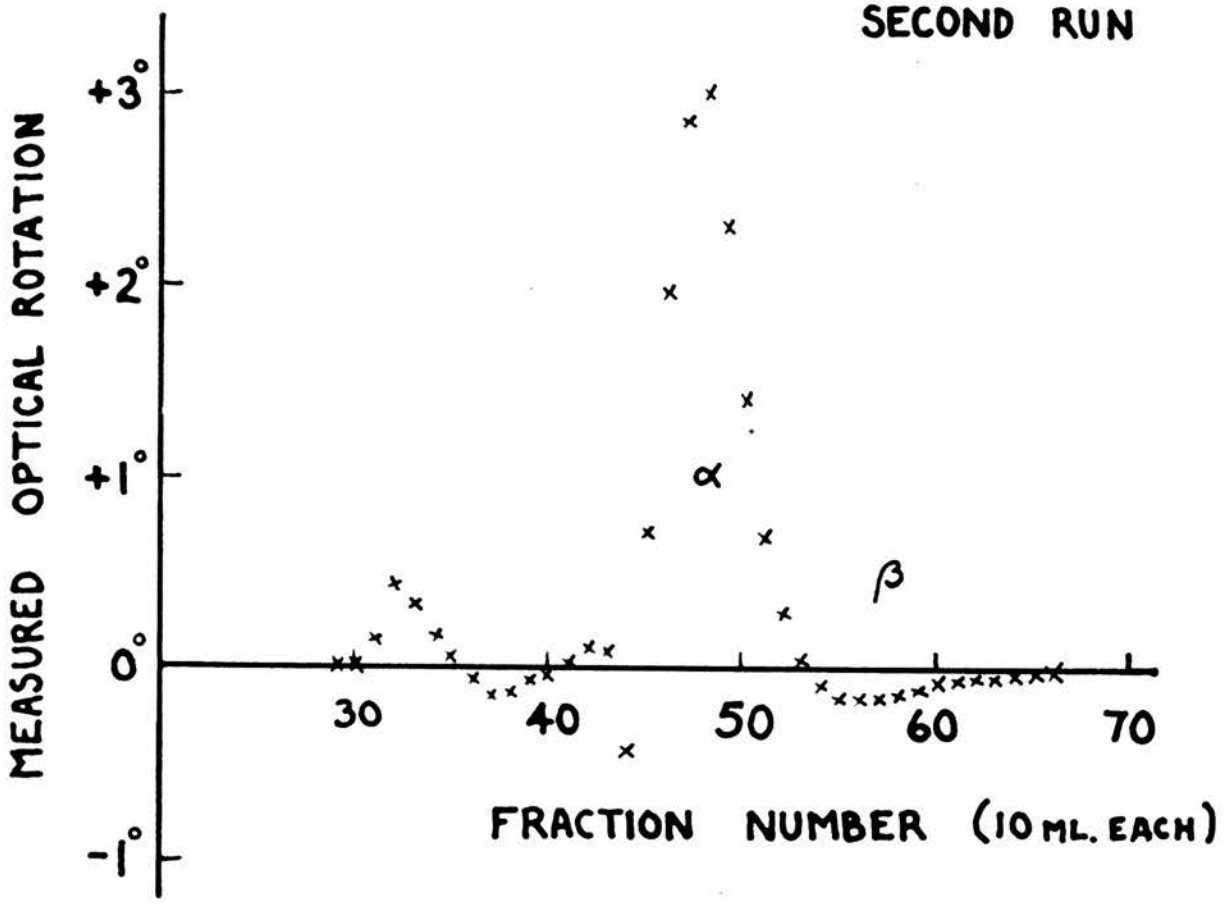


Fig. 5

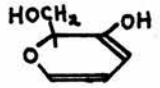
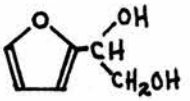
automatically; in the first run of the column 25 ml. fractions were taken, but for the second the volume was changed to 10 ml., so that better separation of the desired glycoside would be obtained. The optical rotation of every fraction containing material was measured and the purity of the fractions containing methyl 2-deoxy-D-galactosides was checked by paper chromatography, using solvent (i), spray (b). The graph of optical rotation vs. fraction number is shown in Fig. 5 for the second run. In fact the corresponding graph for the first run showed the same peaks and troughs, despite the greater fraction volume. However, as expected, the amplitudes of the peaks and troughs were smaller. All the material obtained in the first run was contained in fractions 16 - 31. The last fraction with a positive rotation (No. 25, $\alpha = +0.75^{\circ}$) contained a considerable amount of β-glycoside, and so it was added to the portion of syrup being dealt with in the second run. The distribution of the various components of the mixture among the fractions in the second run is apparent from Fig. 5 .

Evaporation of all the laevorotatory fractions (from both runs) containing only the β-glycoside gave crystals of methyl-2-deoxy-β-D-galactopyranoside (0.64 g.), which on crystallisation from ethyl acetate gave needles (0.49 g.) with m. p. 122 - 123° and $[\alpha]_D^{20}$ -40° (c 1 in MeOH). Recrystallisation from the same solvent gave material with m. p. 123 - 124°, unaltered by further recrystallisation (Found: C, 47.4; H, 7.6; $C_7H_{14}O_5$ requires C, 47.2; H, 7.9%).

Overend, Shafizadeh and Stacey[25] record methyl 2-deoxy-β-D-galacto-pyranoside as being a syrup with $[\alpha]_D^{20}$ 0° (in MeOH), and Hedgley[42] reports a syrup with zero rotation (MeOH) and n_D^{19} 1.4869. Fractions 53 and 54 of the second run contained a little of the α-anomer, despite their negative rotation. On evaporation, these fractions gave syrups, which soon crystallised spontaneously. Recrystallisation from ethyl acetate yielded white needles (0.1 g.) with m. p. 122 - 124° (shrinking at 120°) and $[\alpha]_D^{20}$ -38° (c 1 in MeOH). This material, like that obtained from the pure chromatographic fractions, travelled as a single spot (R_F 0.41) on paper chromatograms, using solvent (i), spray (b). Total yield 3.6%.

Like other β-glycosides,[72] the compound showed no infrared absorption in the region 790 - 850 $cm.^{-1}$ It had ν_{max} 855 (s) and 770 (s) $cm.^{-1}$

Note. The fastest-travelling material appeared in fractions 16 - 18 of the first run and fractions 31 - 35 of the second. It was a liquid with the following properties: $[\alpha]_D$ ca. +24° (c ca. 1 in n-butanol), ultraviolet absorption (in water) λ_{max} 215mμ, ϵ_{max} ca. 7500; λ_{max} 274 mμ, ϵ_{max} ca. 190, assuming molecular weight 128, infrared absorption ν_{max} 1505 (m) $cm.^{-1}$ and 1640-1700 (m) $cm.^{-1}$ The compound travelled as one spot (R_F 0.75) in paper chromatography using solvent (i) and spray (b), and on treatment with benzoyl chloride in sodium hydroxide gave a poor yield of yellowish prisms with m. p. 83 - 85°. When D-glucal[71] and D-galactal[73] were treated with dilute sulphuric acid, a liquid was obtained, which had $[\alpha]_D^{18}$ +15° (in MeOH) and ultraviolet absorption (λ_{max} 215 mμ). It formed a dibenzoate

with m.p. 85° and was taken to be 3-hydroxy-2-hydroxymethyl-pyran  (Molecular weight 128). However, their evidence does not exclude the structure  . Philpott[74] obtained a similar liquid to these mentioned, by the action of methanolic hydrogen chloride (1%) on D-glucal.

(ii) Using the method of Davoll and Lythgoe[38] and Cleaver, Foster and Overend[40] for acetobromo-2-deoxy-sugars, 2-deoxy-α-D-galactopyranosyl bromide triacetate was made by adding hydrogen bromide[54c] (1.09 g., 13.5 mmoles; freed from bromine by bubbling through phenol in carbon tetrachloride) in dried benzene (10 ml.) to distilled D-galactal triacetate (2.00 g., 7.35 mmoles) in benzene (10 ml.) containing benzoyl peroxide (25 mg.), the mixture being cooled under the tap. The solution immediately developed a high positive optical rotation, which rose slowly and was constant after about 20 min., at +26.6° ($[\alpha]_D$ ca. +205°). It was then concentrated at 30° to a pale yellow syrup, which was evaporated with benzene. The product was immediately dissolved in benzene (15 ml.) and to the solution methanol (1 ml.) was gradually added, in the presence of silver carbonate (3.5 g.). More methanol (4 ml.) was added without further reaction occurring, and after storage over the weekend, the solution was filtered and concentrated. The syrupy product was shown by paper chromatography, using system (ii), spray (c), to be a mixture of the methyl 2-deoxy-α- and β-D-galactopyranoside triacetates (R_F 0.50 and 0.35, respectively). Crystallisation from ether-light petroleum gave, with difficulty,

needles of methyl 2-deoxy-β-D-galactopyranoside triacetate (0.21 g., 9%), which had m. p. 82 - 84°, undepressed by an authentic specimen (m. p. 83 - 84.5°) prepared by acetylation of the parent glycoside (20 mg.). Several recrystallisations from chloroform - light petroleum and ethanol-light petroleum gave crystals with m. p. 85 - 86° and $[\alpha]_D^{20}$ -15° (c 2 in $CHCl_3$) (Found: C, 51.1; H, 6.8. $C_{13}H_{20}O_8$ requires C, 51.3; H, 6.6%). Deacetylation with sodium methoxide in methanol, and crystallisation of the product from ethyl acetate-acetone yielded needles with m. p. 120 - 122° (undepressed by an authentic specimen of methyl 2-deoxy-β-D-galactopyranoside) and $[\alpha]_D^{20}$ -38° (c 0.8 in MeOH).

In a later preparation, hydrogen bromide (44 g., 543 mmoles) in benzene (500 ml.) was quickly poured into a cooled solution (ice-water) of the glycal (distilled, 83 g., 305 mmoles) in benzene (400 ml.) containing benzoyl peroxide (1.15 g.). No evolution of heat occurred, but the solution became yellow after a few minutes. The optical rotation was almost the same (+ 25.0°, $[\alpha]_D$ ca. +210°) 30 min. after the addition as at 20 min. The solution was then evaporated at 25° to a syrup, which was twice re-evaporated with benzene, and the pale-yellow product was dissolved in benzene (500 ml.). Silver carbonate (42 g.) was added, followed by the addition, during 5 min., of methanol (50 ml.). Rapid evolution of carbon dioxide occurred, and since heat was given out, the mixture was cooled under the tap. Soon (10 min.) after the addition of methanol more methanol (150 ml.) and silver carbonate (42 g.) were added, without further

reaction occurring. Next day the mixture was filtered, the residue being washed with ethanol, and the filtrate was evaporated down to give a yellow, turbid syrup, which was dissolved in chloroform. Filtration of the solution and evaporation of the filtrate at 30° gave the turbid pale yellow syrup B (ca. 130 g.). Paper chromatography as described earlier (p. 55) again indicated that the product consisted almost completely of roughly equal proportions of the anomeric methyl 2-deoxy-D-galactopyranoside triacetates.

Treatment of syrup B - (1) The bulk of the product was divided into four roughly equal portions. Each was dissolved in a mixture (vol. 50 - 100 ml.) of ether, di-isopropyl ether and light petroleum, the proportions of the solvents being adjusted so that in the refrigerator the solutions did not quite separate into two layers. After seeding of the solutions with authentic β-triacetate, white needles appeared. These slowly accumulated during 3 - 4 weeks, after which time they were filtered off, giving sticky solid (in all 7.73 g.). During recrystallisation from ethanol-light petroleum (20:1, 42 ml.), a small amount of syrup separated, from which the supernatant liquid was decanted. On slow cooling, this deposited long, shiny prisms of the β-acetate (3.10 g., m. p. 85 - 86°).

(2) The remainder of the syrup B (10.0 g.) was chromatographed as follows, using the procedure of Wickberg.[41] A suspension of silica gel (400 g., Hopkins and Williams "M.F.C." grade) in a solution (5% v/v) of dimethyl sulphoxide (DMS) in chloroform was poured into a separating funnel fitted into the top of a chromatographic tube (5.9 x 60 cm.)

containing more of the solvent mixture (1 l.). Without the use of compressed air, (a difference from Wickberg's method) the suspension was run into the tube and allowed to settle, the resulting column of silica being 31 cm. deep. The silica, now impregnated with DMS, was washed with ether (4 l.) 4/5 saturated with a solution (4% V/V) of water in DMS, followed by ether (500 ml.), followed by di-isopropyl ether (1800 ml.) 4/5 saturated with the aqueous DMS, this mixture being the eluent. (In the washing, when a change of solvent was being made, care was taken to prevent the formation of liquid-liquid interfaces. Since DMS is strongly hygroscopic, the separating funnel was kept stoppered to exclude moisture).

Two separations (I and II) were carried out. In each case half (5.0 g.) of the remainder of syrup B was dissolved in the eluent (5 - 10 ml.) and washed on to the column with a further quantity (10 - 15 ml.). Elution was then carried out, using 1800 ml. of eluent. In each case 40 fractions (ca. 45 ml.) were collected. Spotting of each fraction on paper and applying spray (c) showed that in separation I the acetates were contained in fractions 19 - 40, while in II the material was in fractions 15 - 40. This indicates a rapid passage of the compounds down the column, and may explain why a separation of the anomers was not effected, despite the good resolution (relative R_F ca. 1.5) obtainable on paper with a closely similar system (DMS/di-isopropyl ether, (ii), see Appendix (III). Paper chromatography using system (ii), spray (c) indicated that, although complete separation had not been achieved, fractions 29-40 of separation I and 30 - 40 of

II contained only the β-acetate, while fractions 19 - 23 and 15 - 19 (respectively) contained only the α-anomer. Fractions 25 - 29 of separation II appeared to contain β-anomer contaminated with only a trace of α-anomer. Fractions 28 - 40 of separation I and 25 - 40 of separation II were combined and evaporated down to give syrup, from which the bulk of the DMS was removed by dissolution in chloroform (70 ml.) and extraction of the solution with three portions (20 ml. each) of water. The chloroform layer yielded pale yellow syrup (2.7 g.), which crystallised spontaneously. Recrystallisation from ethanol-light petroleum (10:1, 20 ml.), with slow cooling, gave long prisms (1.28 g.) with m. p. 85 - 86°. The mother-liquor yielded less pure material (0.24 g., m. p. 81 - 84°, with softening at 77°). Total recovery 15%. The recovery was slightly poorer (ca. 11%) in a small-scale separation carried out as above, using a column 1.7 cm. in diameter with proportionate amounts of silica (40 g.) and syrup B (0.50 g.). The extent of separation was the same as on the large scale.

Deacetylation of methyl 2-deoxy-β-D-galactopyranoside triacetate (4.36 g., m. p. 85 - 86°) with sodium methoxide in methanol, and crystallisation of the product from ethanol-ethyl acetate (1:30, 31 ml.) gave long, thin needles of methyl 2-deoxy-β-D-galactopyranoside (1.70 g., 67%) with m. p. 123 - 124°. From the mother liquor were obtained crystals (0.42 g., 16%) with m. p. 112 - 118°.

Tosylation. Using the method described previously, methyl 2-deoxy-β-D-galactopyranoside (0.700 g., 3.94 mmoles) in pyridine (10 ml.) was

esterified with tosyl chloride (0.825 g., 4.32 mmoles) in pyridine (15 ml.), more pyridine (5 ml.) being used for rinsing of the separating funnel containing the reagent. After removal of the pyridine by evaporation in the presence of ethanol, the resulting red syrup was dissolved in chloroform (50 ml.) and the solution washed with 0.5 N-sulphuric acid (20 ml.) and aqueous sodium bicarbonate solution (20 ml.). Evaporation of the dried organic layer gave solid, which was crystallised from acetone-light petroleum (2:1, 15 ml.) containing 3% of pyridine. The long wispy needles obtained (0.36 g., 28%) clung together, forming a spongy mass on the filter, but were easily powdered after being dried. They had m. p. 93.5 - 95° (shrinking at 93°), and were shown by thin-layer chromatography, using system (v), spray (e), to contain small amounts of fast-moving impurities. [The mother-liquor yielded crystals (0.10 g., 8%, m. p. 90 - 94°) with a larger proportion of these impurities]. Recrystallisation from acetone-chloroform-light petroleum (3:1:5, 9 ml.) containing 3% of pyridine gave needles (0.225 g.) with m. p. 98 - 99° and $[\alpha]_D^{18}$ -37° (c 2 in $CHCl_3$). These contained only a trace of fast-moving material (R_F 0.68) as shown by thin-layer chromatography, using the above solvents. A second recrystallisation from acetone-chloroform-light petroleum (6:1:10) containing ca. 3% of pyridine gave material with m. p. 96.5 - 97.5, travelling as one spot (R_F ca. 0.05) in thin-layer chromatography, using system (v). (Heavy loading showed no impurity) (Found: C, 50.6; H, 6.2; S, 9.9. $C_{14}H_{20}O_7S$ requires

C, 50.6; H, 6.1; S, 9.6%). In every case the compound melted with bubbling, but without discolouration.

In previous experiments on a smaller scale it was found that recrystallisation in the absence of pyridine lowered the m. p. by ca. 15°, and an attempt to remove the impurities mentioned above by adsorption chromatography on silica gel (as for the 2-deoxy-α-galactoside tosylate, see p.48) was unsuccessful. The solid obtained from this procedure had a very low m. p. and contained a greater proportion of impurities (as shown by thin-layer chromatography) than the material applied to the column.

(e) Methyl 2-deoxy-α-D-glucopyranoside 6-tosylate[42,45,75] Methyl 2-deoxy-α-D-glucopyranoside[39,42,71,74,76,77] was made by two methods.

(i) A solution of 2-deoxy-D-glucose (5 g.) in methanolic hydrogen chloride (2%, 180 ml.) was warmed at 40° for 50 min. Working up in the usual way, by neutralisation with silver carbonate, and crystallisation from ethyl acetate gave, with a little difficulty, large prisms (1.46 g.) with m. p. 91 - 92.5° (unchanged on recrystallisation from acetone) and $[\alpha]_D^{18}$ +135° (c 1 in H_2O). The mother-liquor yielded further material (0.86 g.), with m. p. 91 - 93° and $[\alpha]_D^{21}$ +159° (c 1 in MeOH). These constants agree with the values in the literature, except that Shafizadeh and Stacey[71] report $[\alpha]_D^{20}$ +145° (in MeOH). The infrared spectrum of the compound showed absorption at ν_{max} 870 (s) and 837 (vs) $cm.^{-1}$ Barker, Bourne, Stephens and Whiffen[72] give ν_{max} 877 (s) and 842 (s) $cm.^{-1}$ The material

obtained travelled as a single spot (R_F 0.55) in paper chromatography, using solvent (i) and spray (b). Total yield 44%.

(ii) Methyl 2-deoxy- α -D-glucopyranoside was also made by reduction (with potassium borohydride) of methyl 2-acetoxymercuri-2-deoxy- α -D-manno(?)pyranoside, which was obtained by treatment of D-glucal in methanol with mercuric acetate (see PART II).

Tosylation. Using the previously described method, methyl 2-deoxy- α -D-glucopyranoside (1.31 g., 7.36 mmoles) in pyridine (10 ml.) was tosylated with tosyl chloride (1.55 g., 8.14 mmoles). Methyl 2-deoxy- α -D-glucopyranoside 6-tosylate was obtained by crystallisation from chloroform-light petroleum (1:2) as prisms (1.15 g.) with m. p. 119 - 120.5° and $[\alpha]_D^{18}$ +76° (c 1 in $CHCl_3$). The mother-liquor gave more product (0.25 g.) with m. p. 118.5 - 120° (no decomp.). Yield 57%. The compound travelled as one spot (R_{MT} 2.6) in paper chromatography using system (iv) and spray (h). Hedgley[42] reports m. p. 114 - 115° and $[\alpha]_D^{27}$ +78° (c 0.6 in $CHCl_3$), while Brooks and Overend[75] quote m. p. 120° (decomp.) and $[\alpha]_D$ +77° (c 3.8 in $CHCl_3$). After storage in a desiccator for 6 months the crystals had become dark grey. Recrystallisation as above, after decolourisation with charcoal, gave crystals with m. p. 117 - 117.5° (decomp. after melting), unchanged on further recrystallisation. The compound travelled as one spot (RF ca. 0.6) in thin-layer chromatography (silica) using solvent (vi), spray (e).

(f) Methyl 2-deoxy- β -D-glucopyranoside 6-tosylate.

Methyl 2-deoxy- β -D-glucopyranoside triacetate[37] was made in two ways:- (i) by reduction of methyl 2-chloromercuri-2-deoxy- β -D-

glucopyranoside triacetate, and (ii) from D-glucal triacetate.

(i) Methyl 2-chloromercuri-2-deoxy- β -D-glucopyranoside triacetate (10.83 g., m. p. 171 - 172°) made in the manner described later in Part II was reduced with potassium borohydride in alkaline aqueous dioxan solution, the method also being described later. Methyl 2-deoxy- β -D-glucopyranoside triacetate (4.21 g., m. p. 96.5 - 98°) was obtained as large prisms by crystallisation from ethanol-light petroleum (1:2), further material (0.51 g., m. p. 94 - 97°) being obtained from the mother-liquor. Total yield 77%.

(ii) Acetobromo-D-glucose (m. p. 87 - 88°) was made by the method of Barczai-Martos and Körösy,[63] except that the time of reaction with hydrogen bromide was increased from 1½ - 2 hr. at room temperature to 16 hr. at 0°. When the time given by these authors was used, only α -D-glucopyranose penta-acetate was obtained.

D-glucal triacetate[78] was then made from the acetobromo-sugar by the method already described for the galactose isomer. In a typical experiment the product m. p. 53 - 55°, $[\alpha]_D$ -13° (c 17 in MeOH) was obtained in 75% yield by crystallisation from chloroform-ethanol light petroleum, or from ethanol. Using the method of Davoll and Lythgoe[38] and Bonner,[38] which has already been described [see (d)], hydrogen bromide (6 g., 74 mmoles) in benzene (65 ml.) was added to a solution of D-glucal triacetate (10 g., 37 mmoles) in benzene (35 ml.). After 50 min. the reaction solution was concentrated as before, but the syrupy acetobromo-2-deoxy-D-glucose was dissolved

in dry methanol (75 ml.) instead of benzene, and the silver carbonate (15 g.) was added in portions. Crystallisation of the product from acetone-light petroleum, ether-light petroleum, and from ethanol-light petroleum gave (with some difficulty) methyl 2-deoxy-β-D-glucopyranoside triacetate (2.23 g., 20%), m. p. 93 - 96°, which after recrystallisation had m. p. 96 - 98°, $[\alpha]_D^{18}$ -24° (c 1.5 in $CHCl_3$). A second recrystallisation raised the m. p. to 97.5 - 98.5°, the rotation being unchanged. The m. p. was unaffected by further recrystallisation. Fischer, Bergmann and Schotte report m. p. 96 - 97° and $[\alpha]_D^{19}$ -30° (in acetylene tetrachloride).

Methyl 2-deoxy-β-D-glucopyranoside[37,39] was made by deacetylation of the triacetate in dry methanol containing a catalytic amount of sodium methoxide, the alkaline solution being neutralised before working-up, by stirring with Amberlite resin IRC-50.

A portion (0.87 g.) of acetate made by method (ii) yielded granular crystals of the 2-deoxy-glucoside (0.31 g.) with m. p. 121 - 122° and $[\alpha]_D^{15}$ -48° (c 1 in H_2O). These constants agree with the values in the literature[37,39]. The mother-liquor yielded crystals (0.13 g.) with m. p. 118 - 120°. Yield 85%.

In a subsequent preparation from triacetate (4.70 g.) made by method (i), the deoxy-glucoside was obtained as elongated prisms (1.57 g., 57%, m. p. 120 - 122°). In the infrared spectrum absorption occurred at ν_{max} 901 (s), 889 (s) and 870 (vs) $cm.^{-1}$, there being no absptn. maxima in the region 750 - 850 $cm.^{-1}$ Barker, Bourne, Stephens and Whiffen[72] report identical behaviour for the β-anomer of 2-deoxy-( )-D-glucopyranose, except for the presence of a broad

peak with ν_{max} 812 (m) $cm.^{-1}$ (perhaps due to contamination with α-anomer). The material obtained from both deacetylations travelled as a single spot on paper chromatograms (R_F 0.47), using solvent (i) and spray (b).

Tosylation. Using the methods described previously methyl 2-deoxy- β - D-glucopyranoside (200 mg., 1.12 mmoles) in pyridine (3 ml.) was tosylated with tosyl chloride (240 mg., 1.26 mmoles) in pyridine (3 ml.). After removal of the pyridine by evaporation, dissolution of the resulting syrup in chloroform (10 ml.) and washing of this solution with sodium bicarbonate solution, a syrup was finally obtained , which crystallised spontaneously. Crystallisation from ethanol-light petroleum (1:2) gave needles (194 mg., 52%) with m. p. 124 - 124.5° (decomp.), lowered to 116 - 116.5°, then 114 - 114.5° on further recrystallisations from the same solvent. Recrystallisation of the last mentioned as above, but in the presence of a little added pyridine, raised the m. p. 118 - 118.5°. A final recrystallisation from the same solvent, in the absence of pyridine, produced needles with m. p. 115.5 - 116° (decomp.) (Found: C, 50.8; H, 5.9; S, 9.3. $C_{14}H_{20}O_7S$ requires C, 50.6; H, 6.1; S, 9.6%).

In a subsequent preparation using more of the glucoside (1.57 g.) the last traces of pyridine were removed from the chloroform solution by washing it with aqueous cadmium chloride solution (5%). Needles (1.68 g.) were obtained from benzene-chloroform (3:2) which had m. p. 115.5 - 116° (decomp. after melting) and $[\alpha]_D^{16}$ -42° (c 1.9 in $CHCl_3$). The mother-liquor yielded needles (0.16 g.) with m. p. 116 - 116.5°. Yield 63%. The compound travelled as a single spot in paper chromatography using system (iiia) and in thin-layer

chromatography using solvent (vi) (R_F ca. 0.45) Spray (e) was used.

(g) 1,2-O-ethylene-β-D-glucopyranose 6-tosylate.

2'-Chloroethyl β-D-glucopyranoside tetra-acetate[49,79,80]. Using the method of Coles, Dodds and Bergeim[80] acetobromo-D-glucose (70 g.) was converted into the chloroethyl β-glucoside by dissolution in ethylene chlorohydrin (185 ml. 220 g.), followed by portionwise addition of silver carbonate (84 g.), during 45 min., with cooling under the tap. Stirring was continued at room temperature for 4 hr., after which the mixture was left at 0° for 18 hr. before being filtered. The filtrate was concentrated to 200 ml. Addition of water (700 ml.) then gave the product as needles (47.5 g., 68%) with m. p. 116 - 117.5°. The above authors report m. p. 114°, while Helferich and Lutzmann[79] give m. p. 119 - 120°.

1,2-O-ethylene-β-D-glucopyranose[49,50] was made by the method of Helferich and Werner.[50] The chloroethyl β-glucoside (46.5 g.) was refluxed in aqueous ethanolic (50%) N-sodium hydroxide (1 l.) for 6 hr. After neutralisation of the solution with sulphuric acid and removal of the sodium sulphate-sodium acetate precipitate, concentration of the filtrate and addition of ethanol gave a brown liquid from which needles (A, 28 g.) containing the desired product mixed with sodium salts were obtained on cooling. Further concentration of the mother-liquor and addition of ethanol gave at first only sodium acetate, but then the desired product as elongated prisms (B, 3.60 g.) with m. p. 209 - 211 and $[\alpha]_D^{17}$ +57° (c 1 in H_2O), and finally impure product (C, 5.5 g.). Recrystallisation of B from water-ethanol (1:9) raised the m.p. to 211 - 213° (unchanged by further recrystallisation). Extraction of A and C with acetone in a Soxhlet extractor for 50 hr. gave fine needles of the product in several portions (together 13.5 g.) with m. p.'s in the range 210 - 213°. Yield 73%. The constants obtained agree with the

literature values.

Tosylation. Using the method given earlier, 1,2-O-ethylene-β-D-glucopyranose (1.03 g., 5.0 mmoles) suspended in pyridine (10 ml.) was tosylated with tosyl chloride (1.05 g., 5.5 mmoles) in pyridine (5 ml.). The pyridine was removed by evaporations with ethanol, and 1,2-O-ethylene-β-D-glucopyranose 6-tosylate was obtained by crystallisation from chloroform as fine needles (0.98 g., 54%) with m.p. 170-173°. One recrystallisation from the same solvent gave crystals with m.p. 172-173.5°, and a second gave needles with m.p. 172° and $[\alpha]_D^{18}$ + 33° (c 0.8 in $CHCl_3$) (Found: C, 50.25; H, 5.7; S, 8.9. $C_{15}H_{20}O_8S$ requires C, 50.0; H, 5.6; S, 8.9%).

In a later preparation the 1,2-O-ethylene-sugar (10.30 g.) in pyridine (150 ml.) yielded crystals (12.55 g., 70%) with m.p. 169-171°. Recrystallisation from chloroform-acetone (40:1) gave elongated prisms and needles (11.5 g.) in three fractions, the major one (7.50 g.) having m.p. 172-174° and $[\alpha]_D^{22}$ + 33° (c 1 in $CHCl_3$).

3. Reaction of 1,2-O-Ethylene-β-D-glucopyranose with Sodium Methoxide.

(a) Mild conditions. Powdered 1,2-O-ethylene-β-D-glucopyranose 6-tosylate (1 g., 2.78 mmoles, m.p. 172-174°) was added to 0.5N-sodium methoxide in methanol (20 ml., 10 mmoles). Since a little of the solid remained undissolved, the mixture was shaken for 1½ hr., after which a white suspension of small particles was obtained. The mixture was filtered after standing for 2 hr. The residue (0.15 g., m.p. 159-161°) was shown to be impure starting material by means of its infrared spectrum. The filtrate was diluted with methanol (7 ml.), warmed at 40° on the water-bath for 2 hr., then left at room temperature overnight. The insignificant residue was filtered off and the filtrate evaporated at 30° to give white solid, whichwas then distributed between chloroform (30 ml.) and water (25 ml.). The organic layer yielded starting material (0.25 g. with m.p. 170-171°, 0.38 g. with m.p. 165-168°, neither m.p. being depressed by authentic tosylate). The aqueous layer also gave starting material (0.03 g., m.p. 168-170°). In all ca. 80% of the original tosylate was recovered and sodium tosylate could not be isolated from the reaction mixture.

(b) Vigorous conditions. Powdered 1,2-O-ethylene-β-D-glucopyranose 6-tosylate (0.5 g., 1.39 mmoles) was refluxed in 0.9N-sodium methoxide in methanol (20 ml., 18 mmoles) for 48 hr. and then left at room temperature for 3 days. No solid separated out, apart from a little scum, which was removed by filtration. Evaporation of the filtrate at 30° gave syrup (2 ml.) containing a little white solid. The whole of this mixture dissolved easily in water (10 ml.), and the resulting solution was diluted with water (10 ml.) before being shaken with chloroform (25 ml.).

There was no residue left, when the organic layer had been evaporated to dryness. The aqueous layer was neutralised by passage through a column of weak-acid cation-exchange resin (Amberlite IRC-50). Its optical rotation was then +0.15° (vol. 115 ml.), which corresponds to $[\alpha]_D$ +66°, on the assumption that the sole product of reaction was 3,6-anhydro-1,2-O-ethylene-β-D-glucopyranose. Evaporation of the solution to dryness at 30° gave a hard, tough solid (0.70 g.), which was extracted with chloroform (25 ml.) by standing at room temperature for 3 days, followed by heating briefly at 65°. The mixture was then filtered. Evaporation of the filtrate gave turbid syrup (0.23 g.), which crystallised in 4 hr. Crystallisation from chloroform-light petroleum (2:3, 2.5 ml.) by heating at 50°, cooling to room temperature, and leaving for 5 days, gave granular crystals (A, 40 mg.) with m.p. 167-170° (shrinking from 149-157°). The infrared spectrum (Nujol mull) showed very sharp hydroxyl absorption ν_{max} 3420 cm.$^{-1}$. Although the best reagent for detection of the substances concerned here was (a) (permanganate-periodate), long development times (3 - 20 hr.) were needed, so that paper was unsuitable as a support for chromatography. Instead the thin-layer technique [system (vii)] was used. A travelled as three spots. The largest of these had R_F ca. 0.65, but there was a large amount of 1,2-O-ethylene-β-D-glucopyranose (R_F ca. 0.35) and very little of a compound with R_F ca. 0.45. Evaporation of the mother-liquor of A gave a colourless, mobile syrup (B, 0.15 g.), which could not be crystallised. The syrup had infrared absorption quite similar to that of A, except for having a broad hydroxyl peak and two additional weak, sharp peaks at ν_{max}^{film} 1665 and 1710 cm.$^{-1}$.

Thin-layer chromatography of the syrup showed the presence of the three constituents of A (in different proportions), and in addition a slow-moving substance (R_F *ca.* 0.07). The same results were obtained by using spray (g), which was less sensitive than (a).

The residue (0.49 g.) from the chloroform extraction described was extracted with acetone (100 ml.) in a Soxhlet extractor for 2½ hr. The acetone yielded crystals (20 mg.) which did not melt below 235°, and had an infrared spectrum similar to that of sodium tosylate. The final residue (0.37 g.) of this extraction also had an infrared spectrum like that of sodium tosylate.

4. Sodium Periodate Oxidations

Procedure: (a) In confirmations of structure.

To an appropriate amount of the compound (10-20 mg.) weighed out in a Quickfit R.B. flask (25 ml.) was added 0.025M-sodium meta-periodate solution (5 ml., if the expected uptake was 1 mole of periodate, 10 ml. if 2 moles were expected to be consumed). A blank solution of periodate (5 ml. or 10 ml. as required) was pipetted into a flask and afterwards treated in exactly the same way as the oxidation solution. The weights of the various compounds were chosen so that roughly half of the aliquot of periodate solution (5 ml. or 10 ml.) was reduced to iodate in the oxidation. The flasks were kept in the dark to prevent photo-decomposition of the periodate. Two of the tosylates concerned were very insoluble in water, so shaking overnight was employed, the flasks being covered with black polythene sheet to exclude light. At appropriate intervals samples (1 ml.) of oxidation

TABLE 5.

SODIUM PERIODATE OXIDATIONS IN STRUCTURE CONFIRMATIONS

Compound	Uptake of periodate (moles) after the times given	
1,5-anhydro-D-galactitol 6-Ts	2.07 (23 hr.)	2.13 (45 hr.)
1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-Ts	1.04 (26 hr.)	1.05 (51 hr.)
Me 2-deoxy-β-D-glucopyranoside 6-Ts	0.99 (6 hr.)	1.05 (8 hr.)
Me 2-deoxy-α-D-galactopyranoside 6-Ts	0.70 (2 hr.)	0.70 (3 hr.)
	* 0.99 (1.1 hr.)	1.08 (2.2 hr.)
Me 2-deoxy-β-D-galactopyranoside	1.04 (2.5 hr.)	1.06 (3.7 hr.)
Me 2-deoxy-β-D-galactopyranoside 6-Ts	1.00 (3.8 hr.)	1.00 (5.5 hr.)
1,2-O-ethylene-β-D-glucopyranose	0.99 (24 hr.)	1.02 (46 hr.)
1,2-O-ethylene-β-D-glucopyranose 6-Ts	0.95 (3 days)	1.06 (10 days)
Me α-D-glucopyranoside (control)	1.94 (24 hr.)	2.04 (46 hr.)

Me = methyl Ts = tosylate

* These figures refer to a sample of tosylate prepared by acid hydrolysis of the 3,4-O-isopropylidene-derivative.

solution and of blank were withdrawn and added to a mixture of 0.2N-sulphuric acid (3 ml.) and 0.4N-potassium iodide solution (2 ml.), the liberated iodine being titrated with 0.05N-sodium thiosulphate solution from a micro-burette (5 ml.), using starch indicator.

The procedure was altered slightly for methyl 2-deoxy-α-D-galactopyranoside 6-tosylate prepared from its 3,4-O-isopropylidene-derivative. Methanolic hydrogen chloride (0.05N, 5 ml.) was added to the isopropylidene-compound (ca. 23 mg.) in a Quickfit flask (R.B., 25 ml.). After 3 hr., phosphate buffer (5 ml., made as described on p.72) was added and the solution was evaporated to "dryness" twice in the presence of added water. The residual syrup was transferred to a volumetric flask (10 ml.) containing the periodate solution (5 ml.), and the mixture was made up to the mark. Since both methanol and chloride ion[81] affect periodate, a blank was prepared simultaneously in exactly the same way, only the tosylate being omitted. At suitable intervals, portions (2 ml.) of the solutions were withdrawn and dealt with as described earlier, except that stronger acid (4N-sulphuric acid, 1 ml.) was used, to ensure a low enough pH in the presence of the buffer for complete liberation of iodine.

In the oxidation procedure 1,2-O-ethylene-β-D-glucopyranose 6-tosylate gave fine needles with m.p. 101-104°, but since attempts to recrystallise these from ethanol, water, acetone or aqueous dioxan lowered the m.p., the product was not further examined.

The data for uptake of periodate are given in Table 5. The uptakes (moles of periodate consumed per mole of 6-tosylate)

Table 6. Sodium Periodate Oxidations in Determination of Extent of Cyclisation of 6-Tosylates

Compound	Half-life (min.) of reaction in water.	Time of reaction with NaOH (hr.)	Periodate uptake (moles) after ca. 20 hr.	% of uncyclised material
Me α-D-glucopyranoside (control)	-	-	2.28	114
Me β-D-galactopyranoside 6-Ts (control)	40	18	0.010	0.5%
1,5-anhydro-D-galactitol 6-Ts	2	2	0.006	0.3%
1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-Ts	7.5	3	0.005	0.5%
Me 2-deoxy-α-D-glucopyranoside 6-Ts	42	23	0.010	1%
Me 2-deoxy-β-D-glucopyranoside 6-Ts	57	23	0.014	1.4%
Me 2-deoxy-α-D-galactopyranoside 6-Ts	21	16	(0.037 (*0.017	3.7% *1.7%
Me 2-deoxy-β-D-galactopyranoside 6-Ts	40	24	0.003	0.3%

Me = methyl Ts = tosylate

* These figures refer to a sample of tosylate prepared by acid hydrolysis of the 3,4-O-isopropylidene-derivative.

were determined relative to blank solutions, and methyl α-D-glucopyranoside was used in a control experiment.

(b) In confirmation that the cyclisation of the 6-tosylates with sodium hydroxide was complete.

In every case it was shown (see Table 6.) that the uptake of periodate corresponded to less than 2% of detosylation without cyclisation, except for the specimen of methyl 2-deoxy-α-D-galactopyranoside 6-tosylate obtained directly by tosylation, when the value was 3.7%.

The procedure was similar to that used by Baker[17] for the 6-tosylates of methyl α- and β-D-gluco- and galacto- pyranosides, 1,5-anhydro-D-glucitol and 1,5-anhydro-2-deoxy-D-arabino-hexitol.

To the powdered tosylate (20-25 mg.) in a conical flask (25 ml.) was added (by pipette) aqueous 0.02N-sodium hydroxide solution (10 ml.). Swirling for some time was necessary to dissolve the tosylates. To simulate the conditions employed in the rate measurements (see below, Section 5.), the duration of the alkali treatment was varied in each case to correspond to ca. 15 half-lives of the reaction of the particular tosylate in water. At the end of the time allowed for cyclisation buffer solution (1 ml. of a solution 0.25M with respect to potassium dihydrogen phosphate and to disodium hydrogen phosphate) was added, followed by N-sulphuric acid (0.19 ml.). The pH of the resulting mixture was found to be 6.9 (by pH-meter). At this stage 0.1M-sodium periodate solution (2 ml.) was pipetted into the mixture, which was then left stoppered in the dark for 20-24 hr. Solid sodium bicarbonate (ca. 100 mg.) was then added to the oxidation

solution, followed by 20% potassium iodide solution (4 ml.). The liberated iodine was titrated with 0.0464M-sodium arsenite solution, using a micro-burette (5 ml.) and starch indicator. The uptakes of periodate were determined relative to a blank solution (alkali, acid, buffer and periodate), and in Table 6. are given the data for uptake, calculated in moles per mole of the original 6-tosylate. Methyl α-D-glucopyranoside and methyl β-D-galactopyranoside 6-tosylate were used in control experiments.

Methyl 2-deoxy-α-D-galactopyranoside 6-tosylate prepared from the 3,4-O-isopropylidene derivative was used as well as the specimen obtained by direct tosylation of the parent glycoside. The isopropylidene-compound (ca. 25 mg.) was de-isopropylidenated by the method described earlier (p. 51). After neutralisation of the acid with silver carbonate, Celite was added and the mixture filtered, the residue being washed with ethanol. Evaporation of the filtrate to dryness at 30° and re-evaporation once with water gave a syrup, which was dealt with by the procedure described here.

5. Experimental Procedure in Rate Measurements of the Cyclisation of Sugar 6-Tosylates in Alkali.

(a) Materials

(i) The tosylates were prepared as described earlier, and stored at 0° over calcium chloride. Those not mentioned in detail in Section 2. above had been made previously (1957-59) by Baker.[17]

(ii) The sodium hydroxide was made by dilution of stock 0.1N-solution, which in turn was obtained by dilution (to 500 ml.)

of the contents of ampoules of sodium hydroxide solution (B.D.H. Concentrated Volumetric Solution). Stock solutions, which were not kept for longer than a month, were stored under nitrogen in polythene bottles. The water used for dilution was distilled water, from which ions and carbon dioxide had been removed by passage through an "Elgastat" resin deioniser (Elga Products Ltd.).

Potentiometric titrations of the sodium hydroxide were done, using a pH-meter*, with the exclusion of atmospheric carbon dioxide by passage of nitrogen (carbon dioxide-free) through the solution being titrated. These showed that, despite all the precautions, both the stock 0.1$\underline{N}$-alkali and the 0.02$\underline{N}$-solution contained ca.2% of carbonate. The titrant used was 0.1$\underline{N}$-sulphuric acid solution (also from B.D.H. concentrated solution). The pH of the titration solution was read after each addition (ΔV ml.) of acid, and the ratio ($\Delta pH/\Delta V$) of pH change to volume change for each addition was plotted against the total amount (V ml.) of acid added up to the middle of each addition. Two maxima were obtained, the lower one (at pH ca. 8.5) corresponding to conversion of carbonate to bicarbonate, and the higher (at pH ca. 6) corresponding to conversion of bicarbonate to carbonic acid.

(iii) The 1,4-dioxan used was B.D.H. "Special for Spectroscopy" grade. It was stored in the dark under nitrogen. From one freshly opened bottle, this product had a light transmission of ca. 80% (optical density ca. 0.100) at wavelength 265 mμ, compared with water. From another bottle (one year after being opened) the product had transmission 86.7% (optical density 0.062). B.D.H. "AnalaR" grade and May and Baker "Reagent" grade dioxan had lower transmissions (55% and

* Pye Universal pH-Meter No. 11066

42%, respectively, relative to water), and since a spectrophotometric method was being used for the rate measurements, these products were considered to be unsatisfactory. Purification of B.D.H. AnalaR dioxan by the method of Cavell, Chapman and Johnson[82] gave dioxan with 68% transmission. Freezing is recommended[83] as a good method of purifying dioxan, but when the purified AnalaR product was 90% frozen at 11-12°, the liquid obtained by warming the resulting solid had 71% transmission, only a slight improvement. Since repeated freezing would have been wasteful, and because 71% transmission was too low, the method was abandoned.

By means of potentiometric titrations (as described above) of nominally 0.02N-sodium hydroxide in 50% aqueous dioxan (v/v) with 0.1N-sulphuric acid, it was confirmed that any acidic impurities present in the dioxan did not reduce the concentration of alkali in the mixtures used for rate measurements by more than 2%.

Tests made on dioxan from a freshly opened bottle showed that the light transmission of a solution (0.5N) of sodium hydroxide in 50% aqueous dioxan did not change appreciably during 20 hr. (During this time the optical density of the mixture, relative to water, fell by 0.001, i.e. the transmission increased from 92.0 to 92.2%). However, 10 months later the dioxan from the same bottle became more transparent in the presence of alkali. When this dioxan (5 ml.) was mixed with 0.04N-sodium hydroxide solution (5 ml.) to simulate the conditions used in the rate measurements, the optical density at 265 mμ, relative to water, was constant at 0.057 (corresponding to 87.7% transmission) for over 4 hr., but fell progressively to 0.055 at 20 hr., 0.053 at

48 hr., and 0.051 at 94 hr. after mixing. In all the transmission tests on dioxan calibrated silica cells (1 x 1 cm.) were used.

When equal volumes of water and dioxan are mixed, a contraction in volume (2%) occurs and heat is evolved. The method used for preparation of the reactants (see below) ensured that in the actual reaction mixtures the contraction was only 1%, and since precise comparisons between rates of reaction in water and in aqueous dioxan were not required, no correction was made for this small effect.

(b) Experimental technique in rate measurements. The rates of reaction of monosaccharide 6-tosylates (0.001M) with sodium hydroxide (0.02N) were measured spectrophotometrically at a wavelength of 265 mμ, using a Unicam SP 500 spectrophotometer. Equal volumes of tosylate (0.002M) and base solutions were mixed and the reaction followed by a differential method, by taking readings of the optical density difference (E) between the reaction solution and a suitable blank solution at convenient time intervals.

Details are given below :

(i) The volumetric glassware used was shown by calibration to be well within the tolerances for "Grade B" apparatus.

(ii) Tosylate solutions (ca. 0.002M) were made by dissolution of the compound (15-17.5 mg., depending on the molecular weight of the tosylate) in deionised water or aqueous dioxan (50% v/v), as required, and dilution to 25 ml. in a volumetric flask. The procedure for methyl 2-deoxy-α-D-galactopyranoside 6-tosylate prepared from methyl 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-tosylate was to deisopropylidenate

the latter compound (ca. 20 mg.) by the method given earlier (p. 51). The syrup obtained after neutralisation of the acid used was then evaporated down at 30° once with water (almost to dryness) for cyclisations in water, or once with dioxan (to dryness) for cyclisations in aqueous dioxan.

Owing to its slight solubility in water, a 0.0005M-aqueous solution of methyl α-D-galactopyranoside 6-tosylate was used.

Since the tosylates react slowly with water, the solutions were always used immediately after preparation, and as a precaution the remainder was kept overnight in the refrigerator, if the duplicate run had to be done next day.

(iii) For reactions in water: A portion of tosylate solution (10 ml.) was pipetted into one arm of the two-limbed vessel shown in Fig. 6

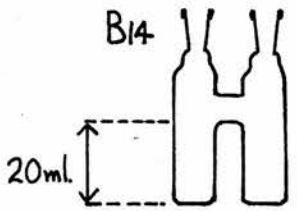


Fig. 6

and the latter was then flushed out with nitrogen (freed from carbon dioxide by passage through a U-tube containing "Sofnolite" absorbent). Sodium hydroxide solution (0.04N, 10 ml.) freshly prepared from stock was pipetted into the other arm. (The same dilute solution of alkali was used for the repeat run).

To prevent the later development of air bubbles, the lightly stoppered mixing vessel was warmed in a water-bath at 40° for 5 min.

For reactions in aqueous dioxan: A portion (10 ml.) of tosylate solution in aqueous dioxan (50% v/v) was pipetted into one arm of the

vessel. Into the other was then pipetted sodium hydroxide solution (0.08N, 5 ml.) freshly made from stock, followed by dioxan (5 ml.). In this way the disturbing effect of the heat of mixing of water and dioxan was avoided. Flushing with nitrogen and expulsion of dissolved air were carried out as above.

(iv) The reactions were followed at wavelength 265 mμ in a stoppered silica cell (1 x 1 cm.) in conjunction with a blank solution (0.001M) of sodium tosylate in water or 50% aqueous dioxan, as required, contained in a similar cell. Owing to the slight solubility of methyl α-D-galactopyranoside 6-tosylate in water, the cyclisation of this compound in water was followed using longer cells (4 x 1 cm.). Since the initial concentration of sugar tosyl ester in the reaction mixture is 0.001M, the same strength as the sodium tosylate in the blank, the optical densities of the two solutions should be practically the same at the end of the reaction, and the reading of the spectrophotometer should be approx. zero. In practice the end-values varied considerably, being mostly in the region 0.01 to 0.04, but occasionally higher. For exceptionally high values, see the Notes on Table 9. The tosylate concentration was chosen as 0.001M, since it gave initial values of the optical density reading of 0.45-0.55 (in water, the value being 0.40-0.45 in aqueous dioxan). As a result, the readings for the early part of the reaction fell in the most accurate region (0.6 to 0.2) of the optical density scale.

The spectrophotometer was provided with a jacketed cell-compartment (SP 570), through which water was pumped from a large bath, containing a Shandon "Circotherm II" thermostat stirring unit, by means

of a Stuart-Turner No.10 circulating pump in the return lead. The thermostat was set so that the temperature in the cell-compartment was $25^{\circ} \pm 0.05$. Although the temperature in the compartment usually varied over a range of only 0.02° during a run, the thermostat could not always be adjusted to 25° exactly. The cell temperature was measured by inserting a thermometer (with 0.1° graduations) through a hole in the compartment lid into a cell filled with liquid paraffin. The thermometer was compared with one calibrated by the National Physical Laboratory (stated accuracy $\pm 0.02^{\circ}$). The apparatus was in a room thermostatted at $22-22.5^{\circ}$, and since the circulating pump heated the water above 25°, the temperature of the reservoir bath was kept down by passing cold tap-water through copper coils placed in it. The rate of flow of the cooling water was adjusted so that the heater in the Circotherm unit switched itself on and off for roughly equal periods of time, since this condition keeps the temperature variation of the system to a minimum.

After the mixing vessel containing the reactants had been kept in the thermostat bath for 20-60 min., the reactants were mixed by repeated inversions (10-20) of the vessel, and the instant of first mixing was noted. The reaction mixture was then transferred to the reaction cell, ready in its compartment, by means of a wide-nozzle pipette (2.5 ml.), and the cell stopper was fitted. All the pipetting was done using a Griffin and George rubber pipette-filler, to exclude carbon dioxide.

(v) The reason for choosing the wavelength of 265 mμ was that this wavelength corresponds to the shoulder of a flat absorption maximum

ULTRAVIOLET SPECTRA OF SODIUM TOSYLATE ----- AND OF METHYL 2-DEOXY-β-D-GLUCOPYRANOSIDE 6-TOSYLATE ———

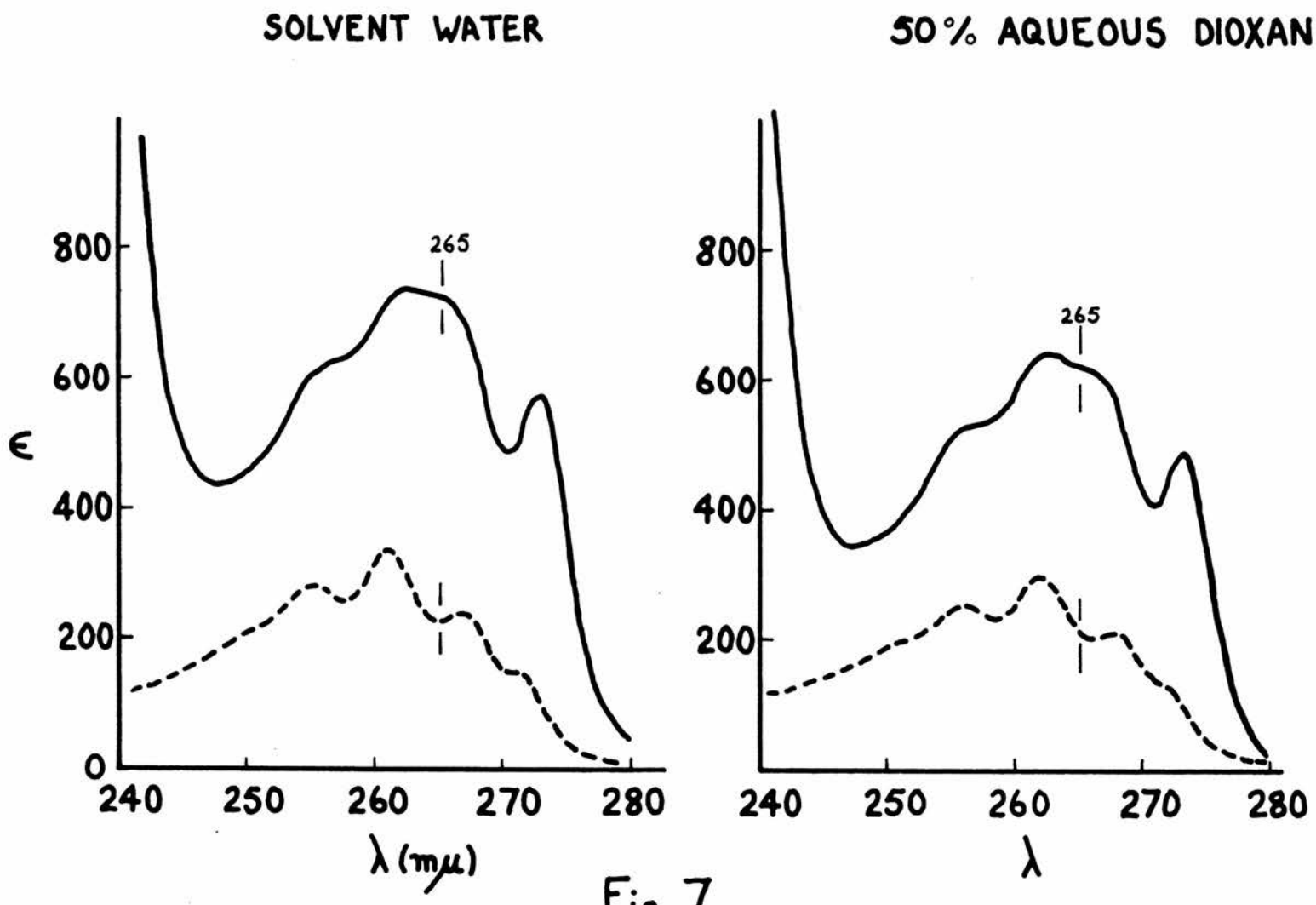


Fig. 7

(water, ϵ ca.730) of tosyl esters and a minimum (ϵ_{min} ca.220) of the tosylate anion. In aqueous dioxan the esters have ϵ ca.620 at 265 mμ, while tosylate ion has ϵ ca.210 at this wavelength, and ϵ_{min} ca.200 at 266 mμ. All the rate measurements were carried out at 265 mμ. The ultraviolet spectra of sodium tosylate and a typical tosyl ester are given in Figure 7 . For each solvent (water and 50% aqueous dioxan) the measurements were made relative to a blank of that solvent. The fact that the initial values of the optical density difference (E) were smaller (ca. 0.45) for reactions done in aqueous dioxan than for water (ca. 0.55) is accounted for by the nature of the spectra.

(vi) Runs for each reaction were repeated only once, since agreement was always good. In each case the reaction was followed for 5-6 half-lives, i.e. to 97-98% completion, by taking readings of optical density (E_t) between reaction and blank solutions at various times t. End-values (E_∞) were obtained after a total of 10-12 half-lives (more than 99.9% reaction). Between 10 and 30 readings were taken during each half-life, in the early stages of reaction. (The frequency decreased as the reaction proceeded). Normally readings were taken at intervals which made the optical density difference between successive readings 0.005 or more. The fastest reaction had a half-life of 1 min., while that of the slowest was 5.5 hr.

(c) Calculation of first-order rate constants

First-order rate constants for the cyclisations were obtained from the readings (E_t) of optical density at times t in two ways.

(i) The usual method, requiring an end-value (E_∞), of plotting

$\log_{10} (E_t - E_\infty)$ *vs.* *t*. This depends on the equation for a first-order process, *viz.* $\log_{10} \frac{E_t - E_\infty}{E_o - E_\infty} = -kt/2.303$ where k = rate constant, and E_o and E_∞ are the initial and final values of the optical density, respectively. Hence a plot of $\log_{10} (E_t - E_\infty)$ *vs.* *t*. gives a straight line with slope $-k/2.303$. Usually the graphs obtained by this method were straight for at least four half-lives.

(ii) The other method was that of Swinbourne[84]. In this pairs of the actual readings $(E_t, E_{t+\Delta t})$, which were separated by a constant time interval (Δt), were plotted one against the other. This procedure gives a straight line with a slope related to the rate constant *k* by the equation $k = \frac{1}{\Delta t} . \ln (\text{slope})$.

No end-value is needed in this method, which is obviously an advantage when, as in the present work, the end-value is uncertain. (See below).

Another procedure which does not require an end-value is that of Guggenheim[85]. In this $\log_{10} (E_t - E_{t+\Delta t})$ is plotted against *t*, giving a straight line with slope $-k/2.303$. The Guggenheim approach was used by R. Baker[17] in his studies of tosylate cyclisation, and a comparison of the two methods is of interest.

Swinbourne's method is more convenient, both because the "unprocessed" data can be used, and because the same scale is suitable for plotting all the reactions, no matter what their rate. A more telling advantage of Swinbourne's method, from the point of view of the present work, is that it biases the early part of the reaction*,

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* Footnote: It was found that half the length of a "Swinbourne" plot corresponded to the first half-life of a reaction.

particularly when the time interval (Δt) is small. (The recommendation of Swinbourne[84] that Δt should be about 0.5-1 half-lives was followed here). Since the readings for the early stages of the reaction occupy the most reliable part of the optical density scale, and since they will be least affected by slow changes in optical density caused by any impurities, the Swinbourne method was thought to be preferable for the present work.

It was found that the "linearity" of end-value plots is a more sensitive test for departures from first-order behaviour than either the Swinbourne or Guggenheim plots.

In some runs the end-value (E_∞) increased slowly, the most marked rise (ca. 0.03 optical density units between 7 and 60 half-lives) occurring in the case of the sample of methyl 2-deoxy-α-D-galacto-pyranoside 6-tosylate obtained by direct tosylation. In cases where the end-value rises, it is possible that even the apparent end-value, i.e. the minimum reading, may be too high, and this could produce appreciable error in the rate constants. In some of the runs done in aqueous dioxan there was a slight downward drift in the end-value, and similar errors might arise here. Because of these complications, the rate constants for each run were calculated by both the Swinbourne and the end-value methods. Since good agreement (usually less than 1% and never more than 5%) was obtained between the rate constants calculated for single runs by the two methods, it is likely that the alterations in end-value did not seriously reduce the accuracy of the results.

Table 7 Rate Data for Reaction of 0.001M, 1,5-Anhydro-2-deoxy-D-arabino-hexitol 6-Tosylate with 0.02N-Sodium Hydroxide at 25° ± 0.05. Solvent 50% Aqueous Dioxan (v/v).

t (min.)	E_t	E_t-E_∞	$2+\log_{10}(E_t-E_\infty)$	t(min.)	E_t	E_t-E_∞	$2+\log_{10}(E_t-E_\infty)$
1	.439	.406	1.609	22	.190	.157	1.196
1½	.438	.395	1.597	23	.1825	.1495	1.175
2	.420	.387	1.588	24	.176	.143	1.155
2½	.410	.377	1.576	25	.170	.137	1.137
3	.401	.368	1.566	26	.164	.131	1.117
3½	.392	.359	1.555	27	.159	.126	1.100
4	.384	.351	1.545	28	.1525	.1195	1.077
4½	.377	.344	1.537	29	.147	.114	1.057
5	.369	.336	1.526	30	.1425	.1095	1.040
5½	.361	.328	1.516	31	.1375	.1045	1.019
6	.354	.321	1.507	32	.133	.100	1.000
6½	.347	.314	1.497	33	.128	.095	0.978
7	.340	.307	1.487	34	.1245	.0915	0.961
7½	.3325	.2995	1.476	35	.1205	.0875	0.942
8	.327	.294	1.468	36	.1165	.0835	0.923
8½	.320	.287	1.458	38	.110	.077	0.887
9	.313	.280	1.447	40	.103	.070	0.845
9½	.3075	.2745	1.439	42	.097	.064	0.806
10	.3005	.2675	1.427	44	.0915	.0585	0.767
10½	.2955	.2625	1.419	46	.086	.053	0.724
11	.2895	.2565	1.409	48	.0815	.0485	0.686
11½	.283	.250	1.398	50	.078	.045	0.653
12	.278	.245	1.389	52	.074	.041	0.613
12½	.272	.239	1.378	54	.0705	.0375	0.574
13	.266	.233	1.367	58	.064	.031	0.491
13½	.2615	.2285	1.359	62	.059	.026	0.415
14	.2575	.2245	1.351	66	.055	.022	0.342
14½	.252	.219	1.340	70	.051	.018	0.255
15	.2475	.2145	1.331	78	.045	.012	0.079
16	.2375	.2045	1.311	86	.0415		
17	.2285	.1955	1.291	94	.039		
18	.220	.187	1.272	110	.035	E_∞ =	0.033
19	.2115	.1785	1.252	126	.033		
20	.203	.170	1.230	150	.0325		
21	.1965	.1635	1.214	180	.0325		

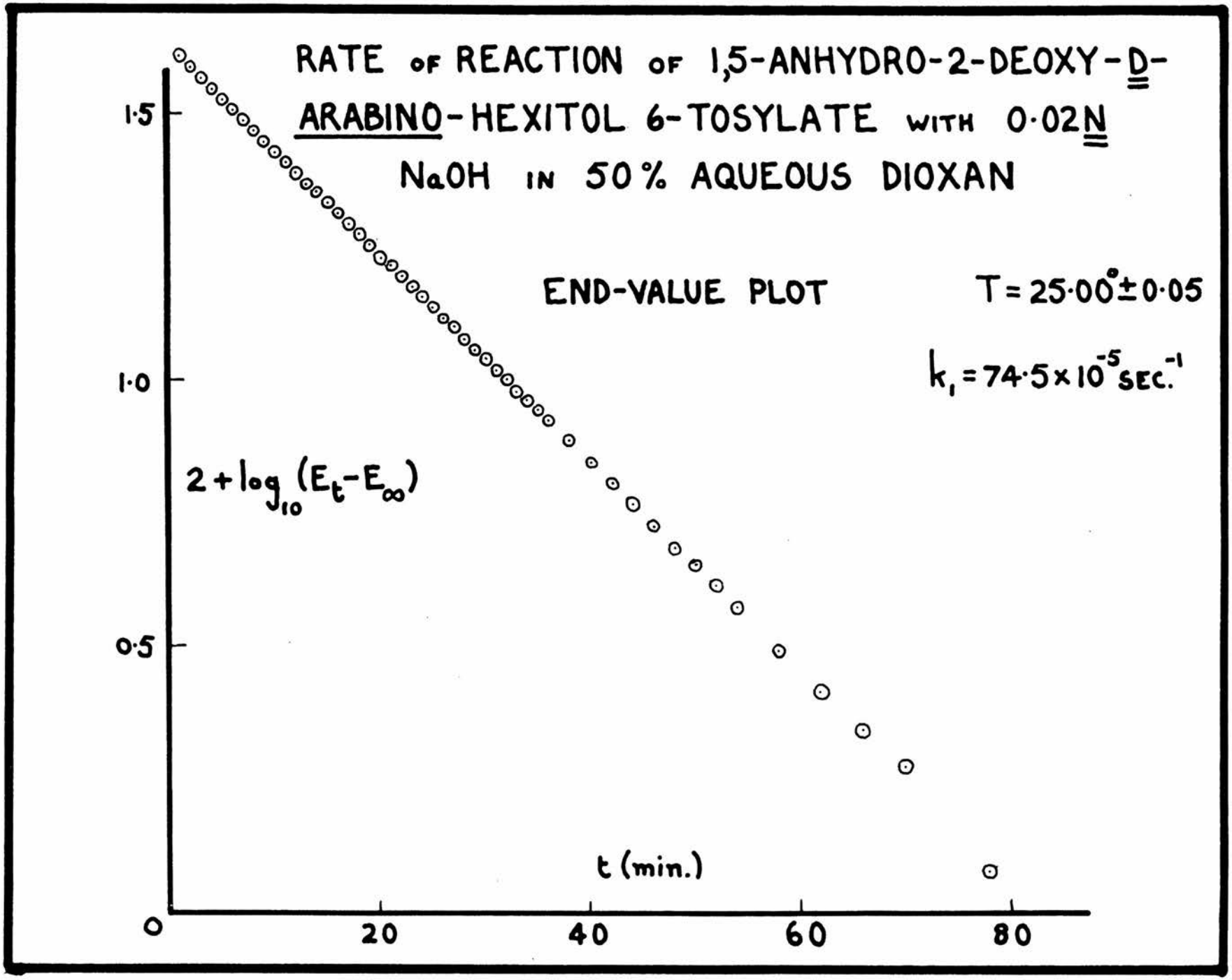
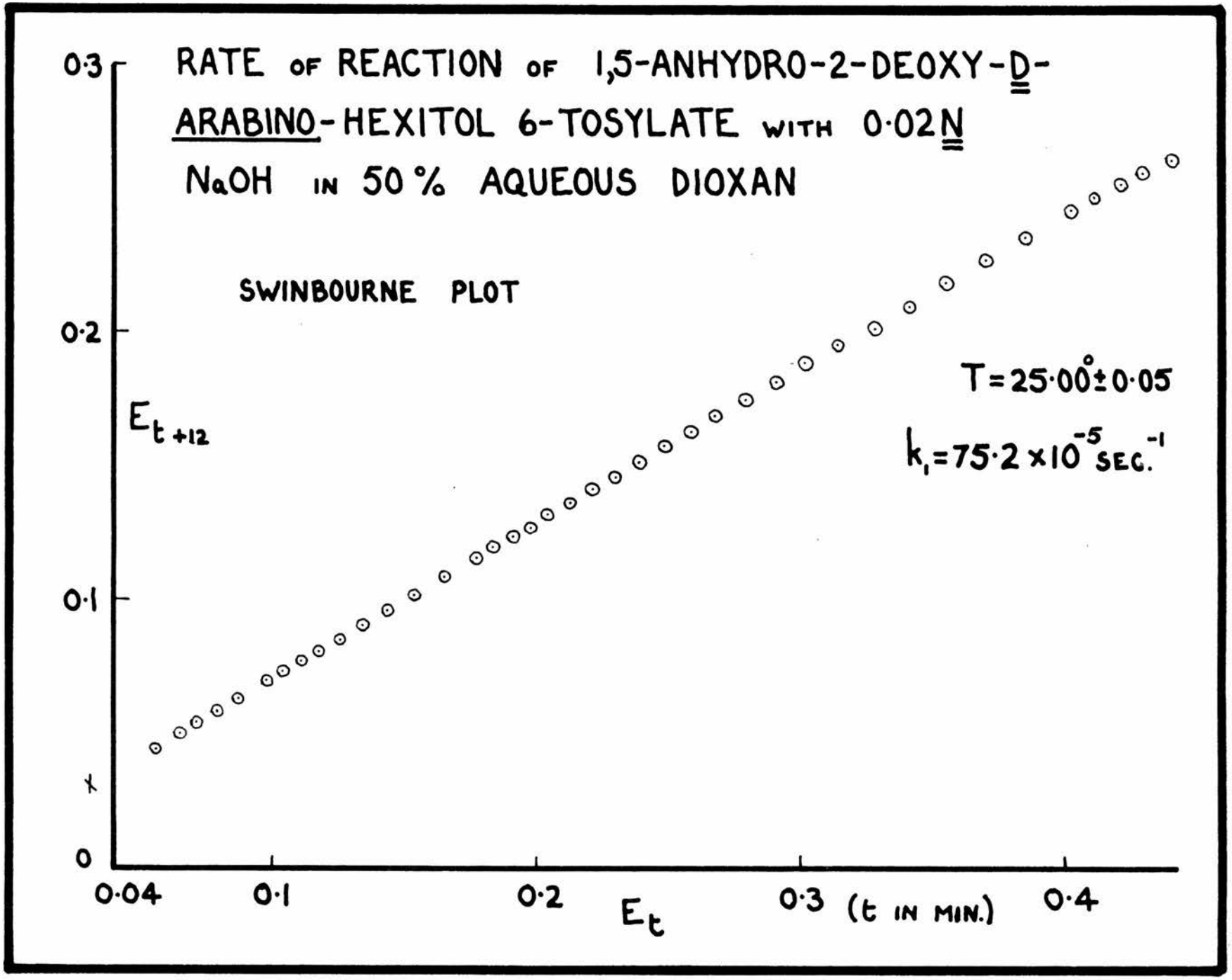

RATE OF REACTION OF 1,5-ANHYDRO-2-DEOXY-D-
ARABINO-HEXITOL 6-TOSYLATE WITH 0·02N
NaOH IN 50% AQUEOUS DIOXAN
END-VALUE PLOT
T = 25·00° ± 0·05
k1 = 74·5 × 10⁻⁵ SEC.⁻¹
2 + log10 (Et − E∞)
1·5
1·0
0·5
0
t (min.)
20
40
60
80

Table 8 "Swinbourne" Data for the Reaction of 1,5-Anhydro-2-deoxy-D-arabino-hexitol 6-Tosylate with Alkali.

t (min.)	E_t	E_{t+12}	t(min.)	E_t	E_{t+12}
1	.439	.266	19	.2115	.1375
1 ½	.428	.2615	20	.203	.133
2	.420	.2575	21	.1965	.128
2 ½	.410	.252	22	.190	.1245
3	.401	.2475	23	.1825	.1205
4	.384	.2375	24	.176	.1165
5	.369	.2285	26	.164	.110
6	.354	.220	28	.1525	.103
7	.340	.2115	30	.1425	.097
8	.327	.203	32	.133	.0915
9	.313	.1965	34	.1245	.086
10	.3005	.190	36	.1165	.0815
11	.2895	.1825	38	.110	.078
12	.278	.176	40	.103	.074
13	.266	.170	42	.097	.0705
14	.2575	.164	46	.086	.064
15	.2475	.159	50	.078	.059
16	.2375	.1525	54	.0705	.055
17	.2285	.147	58	.064	.051
18	.220	.1425	66	.055	.045

Since the half-life is ca. 15.5 min., the interval between the sets of readings ($\Delta t = 12$) is ca. 0.77 X (half-life).

The plot of E_t vs. E_{t+12} is slightly curved.


RATE OF REACTION OF 1,5-ANHYDRO-2-DEOXY-D-ARABINO-HEXITOL 6-TOSYLATE WITH 0·02N NaOH IN 50 % AQUEOUS DIOXAN
SWINBOURNE PLOT
T=25·00°±0·05
k1=75·2×10-5 SEC.-1
0·3
0·2
0·1
0
Et+12
x
0·04
0·1
0·2
0·3
0·4
Et
(t IN MIN.)

The Swinbourne method allows an estimation of the end-value (by extrapolation of the straight-line plot), since when the reaction is complete, $E_t = E_{t+\Delta t}$. In most cases, the values of E_∞ obtained by this procedure agreed with the experimental values to within 0.002.

Specimen data for a typical run are given (Tables 7. and 8.), along with the corresponding end-value and Swinbourne plots. Because of congestion, some of the points in the end-value plot have been omitted from the diagram.

The values of the rate constants obtained by the two procedures are collected in Table 9., and a table of mean values is given in Part A of the Discussion. It will be seen that the agreement between the rate constants for duplicate runs (obtained by either method) was usually less than 2%.

Table 9

Compounds (6-Tosylates)	First-order Rate Constants in Units 10^{-5} sec.$^{-1}$							
	WATER				50% AQUEOUS DIOXAN			
	Swinbourne		End-value		Swinbourne		End-value	
	1.	2.	1.	2.	1.	2.	1.	2.
1,5-anhydro-D-glucitol	52.1[a]	52.1[a]	50.7[b]	50.5[b]	107.9[c]	108.1[c]	105.7[d]	106.0[d]
1,5-anhydro-2-deoxy-D-arabino-hexitol	51.0	50.4	50.3	50.2	75.2[c]	74.6[c]	74.5	73.8
Me α-D-glucopyranoside	5.01[c]	5.02	5.00	4.95	9.94	9.89	9.87	9.87
Me β-D-glucopyranoside[e]	3.33	3.35	3.30	3.34	8.75	8.48	8.73	8.77
Me 2-deoxy-α-D-glucopyranoside	27.2	27.4[cf]	27.3	27.2	33.6[c]	33.4[c]	33.5	33.0
Me 2-deoxy-β-D-glucopyranoside	20.6	20.6	20.1	20.4	27.4	27.8	27.7	27.7
1,5-anhydro-D-galactitol[g]	576	578	583	585	1200	1230	1170[h]	1230[h]
1,5-anhydro-2-deoxy-D-lyxo-hexitol	158	157	157	157	364	374	373	382
Me α-D-galactopyranoside[j]	43.0	42.0	42.8	42.6	77.5	80.6	77.7	77.2
Me β-D-galactopyranoside[k]	29.2	28.6[c]	28.8	28.5	82.7	81.1	81.5	80.5
Me 2-deoxy-α-D-galactopyranoside (i)[m]	54.2	52.6	55.2[n]	54.9[n]	93.5[c]	92.9[c]	90.5[p]	89.8
(ii)[q]	52.0	52.6	51.3[r]	52.1[r]	91.6	91.5	92.0	90.9
Me 2-deoxy-β-D-galactopyranoside[st]	29.1	29.1	28.8	28.6	56.4	56.7	57.0	56.6

Me = methyl (i) By direct tosylation (ii) From 3,4-O-isopropylidene-derivative.

Letters refer to notes on p. 83A,B

Notes on Table 9

(a) Discontinuity in Swinbourne plot - parallel lines obtained.

(b) Discontinuity in end-value plot - two lines of nearly equal slope intersecting at ca. 1.5 half-lives.

(c) Slightly curved Swinbourne plot.

(d) Same as (b), but with intersection at ca. 1 half-life.

(e) For the runs in aqueous dioxan, a fresh solution of tosylate was made for each.

(f) The tosylate solution used for the duplicate was 3 days old.

(g) Owing to the short half-life (1 min.) of the cyclisation in aqueous dioxan, the reaction was 50% complete by the time of the first reading.

(h) The end-value plot showed pronounced curvature towards smaller rate after ca. 2 half-lives. Usually any curvature was in the opposite direction, and not serious.

(j) Unusually high end-values in water (0.067 optical density units in Run 1., and 0.040 in Run 2.).

(k) Same as (j), the values being 0.0665 for Run 1. and 0.0625 for Run 2.

(m) High end-values in water, rising markedly. The values were: 0.110 for Run 1. (rising to 0.137 between 7 and 45 half-lives), and 0.109 for Run 2. (rising to 0.140 between 7 and 60 half-lives). Rather high end-values in aqueous dioxan, falling markedly. The values were: 0.055 for Run 1. (falling to 0.035 between 13.5 and 90 half-lives) and 0.060 for Run 2. (falling to 0.036 between 11 and 105 half-lives).

(n) Pronounced curvature towards greater rate, noticeable after ca. 2 half-lives. (The Swinbourne plots, however, were almost straight).

(p) Curvature to smaller rate appeared in the end-value plot (for Run 1.; apparent after 2 half-lives).

(q) High end-values in water, steady at 0.078 (Run 1., between 11.5 and 52 half-lives) and at 0.079 (Run 2., between 13 and 65 half-lives).

High end-values in aqueous dioxan, rising from 0.094 to 0.107 between 12 and 90 half-lives in Run 1., and from 0.099 to 0.111 between 12 and 115 half-lives in Run 2.

(r) Same as (p), except that the curvature was slight, and only apparent after ca. 3 half-lives.

(s) High end-values in water, 0.082 in both cases, rising very slightly in Run 1. (to 0.085) between 8.5 and 33 half-lives.

In aqueous dioxan the end-values were very high (0.204 and 0.202 for Runs 1. and 2. respectively), but steady for the period of observation (Run 1. was stopped at 65 half-lives, Run 2. at 210 half-lives).

(t) This compound reacted in water, in the absence of alkali, at a rate which was 2% of the rate in 0.02N sodium hydroxide. No allowance has been made for this fact in obtaining the average rate constants (Table 2) for making rate comparisons.

APPENDIX I

Calculation of Dipole Interactions

(a) The object of the calculations given below was to estimate the possible effect of dipole interactions on the preference of the glycosidic methoxyl group in glycosides for the axial or equatorial orientation, and to find out whether the equatorial orientation (normally preferred on steric grounds) is disfavoured as a result of these interactions, in comparison with the axial orientation.

Before details are given, however, the theoretical position must be dealt with. The dipoles concerned here are those associated with the oxygen atom [$O_{(5)}$] of the pyranose sugar ring and that of the glycosidic methoxyl group, and the simplest approach is to consider these oxygens as belonging to saturated aliphatic ether structures. The dipoles will then lie on the bisector of the C-O-C angle and in the plane of the triangle formed by these three atoms. The position and length of the dipole of the C-O-C system are more difficult to assess, and no definite information is available on these points. However, the following is probably a reasonable approach.

It has been shown[86a,87] that in "triangular" molecules like water, alcohols and ethers, the predominating factor contributing to the total dipole moment of the molecule is associated with the two lone pairs of electrons of the oxygen atom. Because of the partial hybridisation of all the oxygen atomic orbitals, which results from

bond formation, the lone-pair p-orbitals are distorted in such a way that their centroids are no longer at the oxygen nucleus, but are on the far side of it from the atoms to which the oxygen is bonded. The centroids of negative and positive charge in the atom (and the molecule) are therefore different, with the existence of a dipole as the consequence. Since this "lone-pair" factor outweighs all the other effects which contribute to the total dipole moment of ethers etc. (or, as in the present case, ether moieties of molecules), it is reasonable to assume that the dipole of ethers is quite short, and lies within the oxygen atom, probably on the far side of the oxygen from the carbons linked to it.

Although it is obviously a drastic over-simplification of the situation, it was further assumed, for the purpose of the calculations, that the dipole of etheric oxygen is a point dipole, placed at the oxygen nucleus, and as stated above, lying in the plane of the triangle formed by the oxygen atom and the two carbons bonded to it, and bisecting the C-O-C angle. This assumption of point dipoles makes the calculations simpler, since the formula used (see below) is strictly valid only for the interaction of dipoles which are infinitesimally short compared with the distance separating them.

(b) Calculations. The energy (E) of interaction of two dipoles (A and B) can be calculated from the formula[88]:

$$E = (\sin\theta_a . \sin\theta_b . \cos\phi - 2\cos\theta_a . \cos\theta_b) . \mu_a\mu_b/\epsilon r^3 \qquad (1)$$

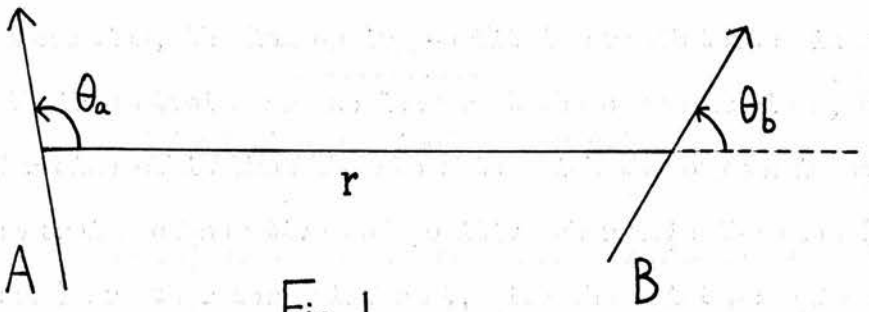


Fig. 1

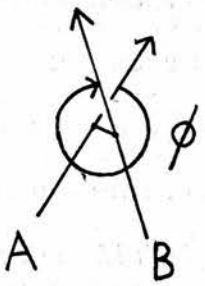


Fig. 2

where μ_a and μ_b are the dipole moments of the dipoles A and B, r is the distance between their mid-points, and ϵ is the dielectric constant of the medium between the dipoles. The arrow-heads represent like-charged ends of the dipoles. θ_a and θ_b are the angles between the dipoles and the line joining their mid-points, measured anticlockwise as shown, and ϕ is the angle, measured clockwise, between the projections of the lines of the dipoles on a plane normal to the line joining the mid-points, dipole B being nearer the viewer and dipole A being used as the reference line. (See Fig. 2). When the value of E is negative, there is an attraction between the dipoles; when its value is positive, there is a repulsion.

As stated above, the dipoles concerned are those of the etheric groups $C_{(5)}-O_{(5)}-C_{(1)}$ and $C_{(1)}-O_{(1)}-CH_3$. The value of the dipole moment of oxygen in aliphatic ethers[86b] is ca. 1.2 D, i.e.

1.2×10^{-18} e.s.u. of energy. From tables of molecular dimensions[89] the value of the $O_{(5)}$-$C_{(1)}$-$O_{(1)}$ angle in α-glucopyranose is 112° and the length of the $O_{(5)}$-$C_{(1)}$ bond is 1.42 Å. The length of the $C_{(1)}$-$O_{(1)}$ bond in methyl glycosides has been taken as the same. Using these values the distance ($\underline{r}$) between the centres of $O_{(5)}$ and $O_{(1)}$ is 2.36 Å, which is also the distance between the oxygen dipoles, on the assumption made earlier about their location. The value of $\underline{r}$ is of course the same for axial or equatorial glycosidic methoxyl groups, in either chair conformation.

The quantities described so far are obviously the same for all conformations of the sugar ring and of the $O_{(1)}$-CH_3 bond. But the magnitude and even the sign of the interaction between the dipoles will obviously be determined by the conformation of the $O_{(1)}$-CH_3 bond with regard to rotation about the $C_{(1)}$-$O_{(1)}$ bond, and in this respect there is no reason to believe that the resulting interaction will be the same for axial and equatorial orientations of the methoxyl group.

The conclusions made from the calculations arebased on the assumption that the actual positions adopted by the $O_{(1)}$-CH_3 bond for axial and equatorial methoxyl are those for which the steric interactions suffered by the methyl group are least. However, it was thought desirable to calculate the dipole interactions for various orientations of the $O_{(1)}$-CH_3 bond, both for axial and equatorial methoxyl. It is clear that the variations occurring in dipole interaction as the $O_{(1)}$-CH_3 bond is rotated are expressed by the trigonometric factor $(\sin \theta_a . \cos \theta_b . \cos \phi - 2 \cos \theta_a . \cos \theta_b)$ in Formula (1) above, and before

an account is given of this aspect of the calculations, it is appropriate to consider first the value of the constant term, viz.

$$\mu_a\mu_b / \epsilon r^3.$$

The value of ϵ (the dielectric constant of the medium separating the dipoles) is not certain, since the value of the dielectric constant inside a molecule will be less than the bulk dielectric constant of the medium (in this case solvent) surrounding the molecule. Kirkwood and Westheimer[90] suggested that in cases like this the "internal" dielectric constant of a molecule should be taken as ca. 2 and this approach has been followed by other authors, for example Allinger and Allinger[91], who used $\epsilon = 2$ in calculations of the energy of interaction of the C=O and C-Br dipoles in 2-bromocyclohexanone, and Bell and Wright[92], who assumed $\epsilon = 3$ in making dipole calculations on potassium carboxylate sulphonates. In the present work ϵ is taken as approximately 2. (It should be said that the value of the "molecular" dielectric constant would still be expected to vary somewhat with changes in the dielectric constant of the solvent, so that the arguments advanced in the Discussion about the effects of altering the solvent are valid). The values $\mu_a = \mu_b = 1.2 \times 10^{-18}$ e.s.u. of energy, $r = 2.36\text{Å} = 2.36 \times 10^{-8}$ cm. (measurements on the molecular model described below gave the value 2.42 Å), and $\epsilon = 2$,

give $$\frac{\mu_a\mu_b}{\epsilon r^3} = \frac{(1.2 \times 10^{-18})^2}{2 \times (2.36 \times 10^{-8})^3}$$ e.s.u. of energy/molecule, i.e. ergs/molecule

$$= \frac{1.2^2 \times 10^{-12}}{26.4} \times \frac{6 \times 10^{23}}{4.2 \times 10^7 \times 10^3}$$ kcals./mole.

$$= 0.78 \text{ kcals./mole.}$$

The actual values of the interactions will then be this amount multiplied by the values of the trigonometric expression in (1) for the various orientations of the $O_{(1)}$-CH_3 bond.

The calculation of the values of the trigonometric factor will now be described. A model of the pyranose sugar ring was made up with ball and rod components obtained from Crystal Structures Ltd., Cambridge. The balls (wooden) were 1 in. in diameter and had 26 sockets ready drilled in each, these being set so that the rods (thick brass) could be fitted in to give a great variety of bond angles. The rods were supplied in lengths which made the scale of the bonds 2 in. to 1 Å. The length of C-C bonds was equivalent to 1.54 Å and that of C-O bonds was 1.40 Å. A thin wooden rod, cut to the right length, was used to mark the line joining the point dipoles at the centres of $O_{(5)}$ and $O_{(1)}$, and to show the direction of the dipoles, rods were inserted into appropriate sockets in the balls. In the model, as expected, the ring-oxygen dipole remains fixed at an angle (θ_a) of 90° to the line $O_{(5)}$-$O_{(1)}$ joining the dipoles, in the case of an equatorial methoxyl group (see Fig. 3), and at 140° for an axial methoxyl. The procedure adopted was to measure the angles (θ_b) between the direction of the $O_{(1)}$-dipole (μ_b) and the line $O_{(5)}$-$O_{(1)}$ at twelve orientations of the $O_{(1)}$-CH_3 bond (30° intervals), and the corresponding values of ϕ.

Equatorial methoxyl

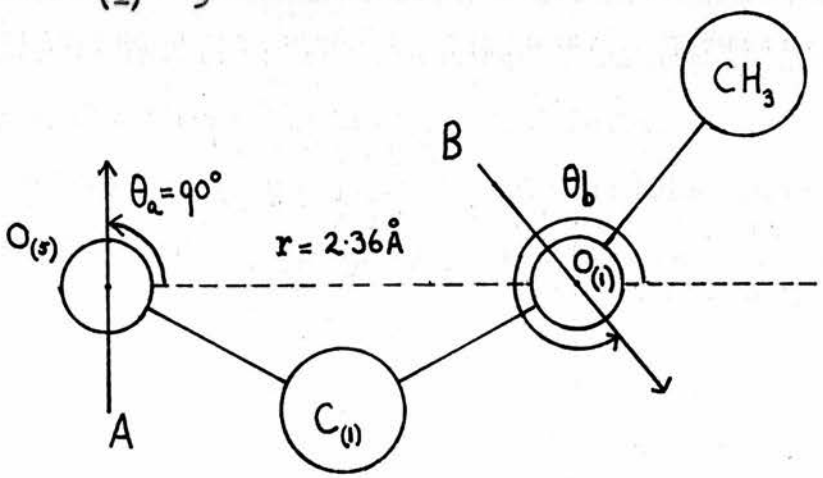


Fig. 3

CONTRIBUTIONS OF $O_{(1)}-O_{(5)}$ DIPOLE INTERACTIONS TO THE FREE ENERGY OF GLYCOSIDES, AT VARIOUS ORIENTATIONS OF THE $O_{(1)}-CH_3$ BOND

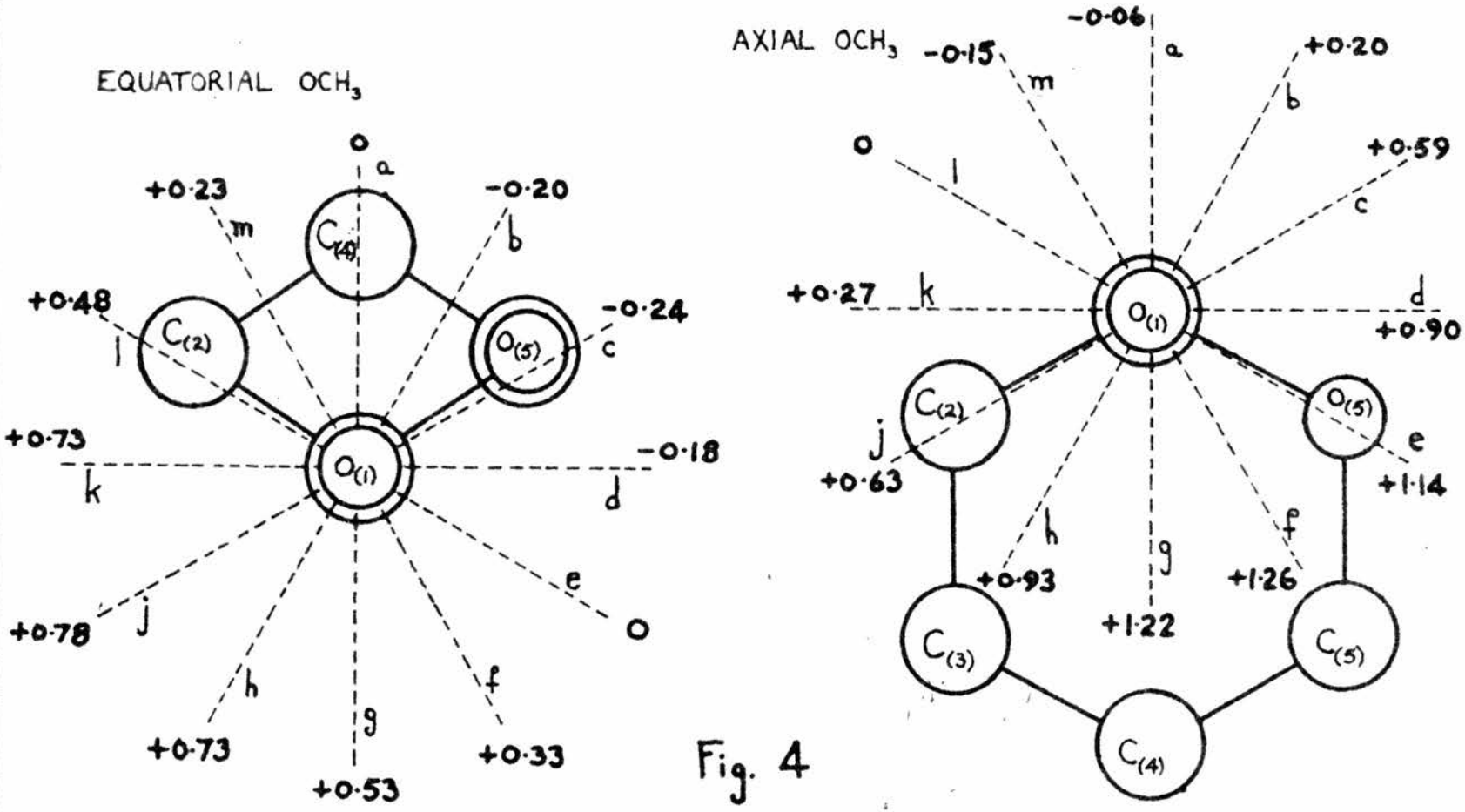


Fig. 4

LOOKING DOWN THE $O_{(1)}-C_{(1)}$ BOND IN EACH CASE.

LINES RADIATING FROM $O_{(1)}$ SHOW THE ORIENTATIONS OF THE $O_{(1)}-CH_3$ BOND.

POSITIVE NUMBERS REPRESENT REPULSION, NEGATIVE NUMBERS ATTRACTION, IN KCALS./MOLE.

starting at $\phi=0^{o}$. This was done for both axial and equatorial methoxyl. (The angles were measured with a protractor cut so that when the instrument was fitted over one of the ball-atoms, its origin coincided with the atomic nucleus). With the values so obtained, a set of values of ($\sin\theta_a.\sin\theta_b.\cos\phi - 2\cos\theta_a.\cos\theta_b$) was prepared for the various orientations of the $O_{(1)}$-CH_3 bond, for both the axial and equatorial methoxyl cases. These values, multiplied by the value (0.78 kcals.) of the constant term ($\mu_a\mu_b/\epsilon\, r^3$) in the expression for $\underline{E}$, are shown in Fig. 4, alongside the orientations of the $O_{(1)}$-CH_3 bond to which they correspond. These patterns of variation of energy contribution apply to either chair conformation of the ring.

The axial and equatorial cases will now be considered in detail. In the case of equatorial methoxyl in the C1-conformation, orientations k, l, m, a, b, c, d and e are obviously strongly hindered sterically by interactions of the methyl group with the axial hydrogen on $C_{(2)}$ (axial hydroxyl on $C_{(2)}$ in the 1C-conformation) and the vacant p-orbitals of the ring oxygen, which are large enough to cause steric hindrance. In addition, orientation j will be unfavoured, because of a strong interaction with equatorial OH (or H) on $C_{(2)}$, and orientation g will be unfavoured by eclipsing of the methyl group with $H_{(1)}$. This leaves orientations f and h as the sterically favoured ones and, as the diagram shows, these positions are disfavoured strongly by dipole interactions. Hence the C1-conformation of β-glycosides and the 1C-conformation of their α-anomers (equatorial methoxyl in each) will be disfavoured by dipole interactions.

In the case of axial methoxyl, similar considerations indicate that the sterically favoured orientations of the $O_{(1)}$-CH_3 bond are m and b. Of these (m) actually corresponds to a dipole attraction, so that this orientation is favoured by both steric and dipole effects. Hence it is likely that the C1-conformation of α-glycosides and the 1C-conformation of β-glycosides are favoured by dipole interactions (or at least not disfavoured).

Summing up, the above (tentative) conclusions imply that dipole interactions will provide a retarding factor in the conformational change (C1 to 1C) of α-glycosides (methoxyl going from the axial, favoured, to the equatorial, disfavoured orientation), and an equal accelerating factor in the conformational change of β-glycosides.

The above calculations are obviously crude, bearing in mind the doubt there is about the correct value of the dielectric constant to use and the lack of precision with which the effective orientation of the $O_{(1)}$-CH_3 bond of the glycosidic group can be assessed. Further uncertainties are brought in by the lack of information concerning the position and length of the oxygen dipoles, (which are certainly not point dipoles[93]). Although the molecular model used in the present case was not highly accurate regarding bond lengths and especially bond angles (in the model, the $O_{(5)}$-$C_{(1)}$-$O_{(1)}$ angle was 110° and the $C_{(1)}$-$O_{(1)}$-CH_3 angle was 106°), it is unlikely that materially different conclusions would be reached by using a better model. The chief uncertainties in the calculations lie in the assumptions which have to be made.

APPENDIX II

Treatment of Pseudo-unimolecular Rate Data

(i) The study of bimolecular reactions is often expedited by employing a large excess of one reactant, so that the observed kinetics are first-order and the derivation of the rate constant is simplified. This approach was used in the present work and in that of Baker[17]. It is often assumed that a 9-fold excess of one reactant is sufficient to make a bimolecular reaction pseudo-unimolecular (*i.e.* show first-order kinetics), but the considerations below show that such an assumption is not strictly valid, even for the 19-fold excess used in the present work.

Artificial data for a second-order reaction were calculated, with the initial concentration (a) of one reactant (A) 20 times the concentration (b) of the other (B). A plot of $\log_{10}\left[a\,(b-x)/b(a-x)\right]$ *vs.* *t*, where x = no. of moles of each reactant consumed at time *t*, gave a straight line, as expected for second-order kinetics. But when $\log_{10}(b-x)$ was plotted against *t* on the same scale as the kinetic runs in the present work, the resulting graph was, unexpectedly, curved slightly. The curvature was just detectable after three half-lives, and was towards lower rate as the later stages of "reaction" were approached. However, in the actual runs curvature of this type was obscured by random error. In fact, in the later stages of reaction curvature in the opposite direction was usually observed (presumably because of rising end-values, see PART I, Experimental, 5.).

When pairs of values $(b-x)_t$, $(b-x)_{t+\Delta t}$, Δt being constant, were obtained from a graph of (b-x) *vs.* t and plotted against each other according to the Swinbourne method[84] (with Δt = 0.85 half-lives), a straight line was obtained. The result was the same with the Guggenheim method[85]. A plot of $\log_{10}\left[(b-x)_t - (b-x)_{t+\Delta t}\right]$ *vs.* t, with t = 2.5 half-lives, was a straight line. The interesting point is that the first-order rate constants derived from the Swinbourne and Guggenheim plots and from the early, straight part of the end-value plot (the first three half-lives) were all *ca.* 2% lower than the "first-order" rate constant derived from the true second-order plot (by multiplying the second-order rate constant by the initial concentration of A). Nevertheless, the first-order treatment was used in the present work, because of its simplicity and because precise absolute data for the rates were not necessary.

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PART II

MERCURY-COMPOUNDS OF SUGARS.

TABLE OF CONTENTS FOR PART II

DISCUSSION

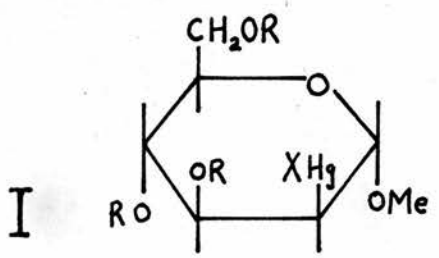
Mercury-compounds of Sugars

The work described here was done to obtain better methods for preparing the methyl 2-deoxy-α- and β-D-glucopyranosides necessary for synthesis of 6-tosylates for kinetic studies. Both compounds have previously been prepared from D-glucal, via 2-deoxy-D-glucose, by two-stage[1,2] and five-stage[3] syntheses respectively, the overall yields being ca. 20% and ca. 15%. A four-stage synthesis of the β-anomer from D-glucal triacetate with an overall yield of ca. 10%. has also been described.[4]

A major factor limiting the yields in syntheses via 2-deoxy-D-glucose is that the hydration of D-glucal to the 2-deoxy-sugar is complicated by the formation of an unsaturated by-product.[5] Despite a report by Hughes, Overend and Stacey[2] that methyl 2-deoxy-α-D-glucopyranoside can be obtained in 59% yield by the acid-catalysed addition of methanol to D-glucal, this reaction gave unpromising results. In addition to the conditions used by the above authors[2] the following were also tried:- 0.9% methanolic hydrogen chloride at 60° for 1¼ hr., 0.2% methanolic hydrogen chloride at room temperature for 16 min. and for 19 hr. All these attempts were equally unsuccessful. The infrared spectra of the products showed C=C or C=O absorption, or both. Paper chromatography of the reaction products, using solvent (i) with sprays (a) and (b), showed that, in addition to the 2-deoxy-α-glucoside and a little of the β-anomer,

several fast-moving by-products (not identified) were present. These evidently prevented crystallisation of the desired glucoside. It has already been noted[6,7] that large amounts of a furan derivative are produced when this reaction is carried out under milder conditions.

In view of the complications which seem to beset acid-catalysed additions to D-glucal, it appeared profitable to investigate indirect methods of adding methanol to the double bond, e.g. methoxymercuration[8,9] followed by reduction [.CH:CH. ⟶ .CH(HgOAc).CH(OMe). ⟶ .CH_2.CH(OMe).]. Since the methoxymercuration of D-glucal can be regarded[8,9,10] as a typical electrophilic addition to a vinyl ether, it was anticipated that the mercury atom and methoxyl group would become attached to $C_{(2)}$ and $C_{(1)}$ respectively, and that trans-addition would occur. (The trans-configuration of the product of methoxymercuration of cyclohexene has recently been established[11] by nuclear magnetic resonance spectroscopy. However, Wright and his co-workers[12] have expressed a contrary view of methoxymercuration. They point out that earlier X-ray evidence[13] for the occurrence of trans-addition in the methoxymercuration of cyclohexene is inconclusive). Hence the most likely products in methoxymercuration of D-glucal are methyl 2-acetoxymercuri-2-deoxy-α-D-mannopyranoside (I; R = H, X = OAc) and the β-D-gluco-isomer (II; R = H, X = OAc). The former



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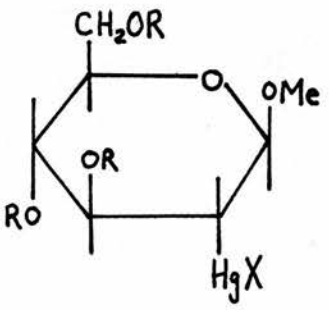


II

compound might be expected to predominate, since it would be formed by di-axial addition[14] to the more stable half-chair conformation of D-glucal, which has $C_{(6)}$ and $O_{(4)}$ equatorial, and $O_{(3)}$ quasi-equatorial.

In fact, optical rotation measurements showed that D-glucal reacted rapidly with mercuric acetate in methanol and a crystalline methoxymercuriacetate was isolated in 60 - 70% yield. On reduction with potassium borohydride in the presence of alkali, this gave methyl 2-deoxy-α-D-glucopyranoside, which was freed from borate by acetylation[15]. Reduction with sodium in ethanol or sodium amalgam, or hydrogenation with Raney nickel catalyst resulted in the formation of unidentifiable products, besides small amounts of D-glucal and the expected methyl 2-deoxy-α-D-glucopyranoside.

The configuration at $C_{(1)}$ in the mercuriacetate is therefore established and, if trans-addition is assumed, the compound must be methyl 2-acetoxymercuri-2-deoxy-α-D-mannopyranoside (I; R = H, X = OAc), the isomer expected on conformational grounds. To confirm this, Dr. H.W.W. Ehrlich kindly undertook an X-ray examination of the compound. Unfortunately this proved unpromising (see Experimental). Attempts were made to prepare the corresponding mercurichloride and mercuribenzoate in the hope that these compounds might be more suitable for X-ray structure determination; however only syrups were obtained when a solution of the mercuriacetate in methanol was percolated through a column of Amberlite IRA 400 resin in the chloride or benzoate form.

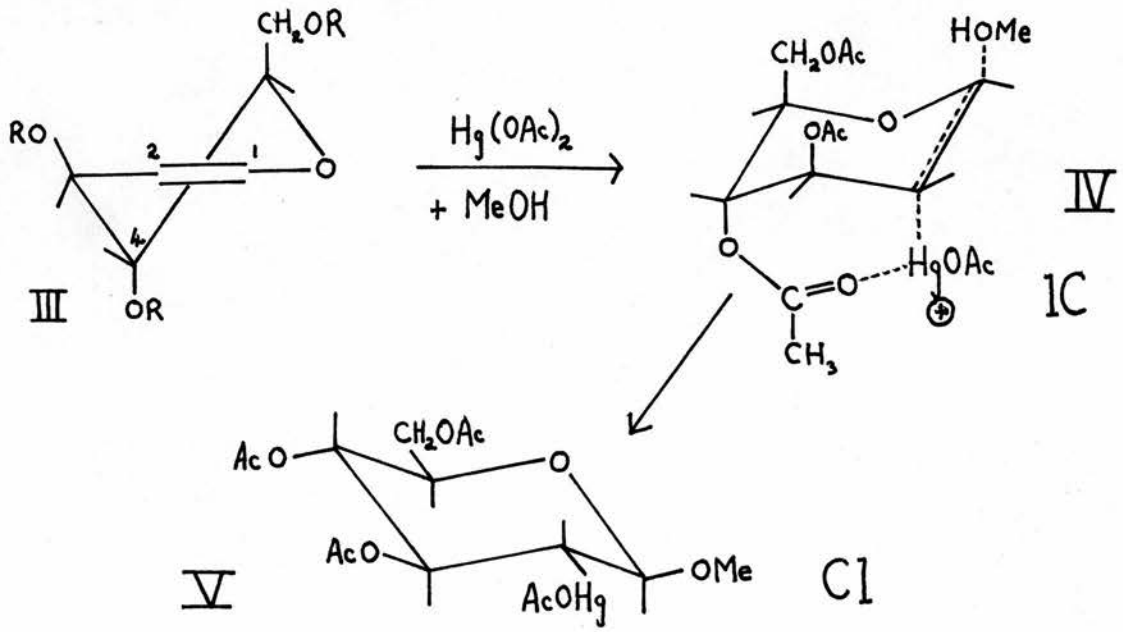
The procedure described above provides a convenient route to methyl 2-deoxy-α-D-glucopyranoside, the overall yield from D-glucal being 45 - 50%. When the reduction was carried out without prior isolation of the mercuriacetate, the overall yield was 32%. Paper chromatography and optical rotations indicated that only a small proportion of methyl-2-deoxy-β-D-glucopyranoside was formed in the latter reduction, showing that the methoxymercuration is highly stereospecific.

The reaction of D-glucal triacetate with mercuric acetate in methanol was also studied. The syrupy product was clearly a mixture, and although a solid mercuriacetate (m. p. variable) could be obtained from it in poor yield, it was found to be more convenient to replace the ionic acetate by chloride. This yielded two crystalline mercurichlorides. The less soluble (dextrorotatory, 38% yield) was shown by an X-ray analysis, kindly undertaken by Dr. H.W.W. Ehrlich[16], to be methyl 2-chloromercuri-2-deoxy-β-D-glucopyranoside triacetate. (II; R = Ac, X = Cl). This agrees with the assumption made earlier that methoxymercuration is a *trans*-addition. Reductive demercuration of this mercurichloride with potassium borohydride in the presence of alkali was accompanied by deacetylation and yielded methyl 2-deoxy-β-D-glucopyranoside, which was isolated as the triacetate. This confirms the stereochemistry at $C_{(1)}$ and constitutes a convenient preparation of methyl 2-deoxy-β-D-glucopyranoside, the overall yield of the triacetate from D-glucal triacetate being 28%. Reduction of the mercuration solution without separation of the mercurials gave the same yield of methyl 2-deoxy-β-D-glucopyranoside triacetate.

The second, more soluble isomer (laevorotatory, 47% yield) is probably methyl 2-chloromercuri-2-deoxy- α-D-mannopyranoside triacetate (I; R = Ac, X = Cl). On reduction it gave a solution with a high positive optical rotation, from which methyl 2-deoxy- α-D-glucopyranoside was isolated in 42% yield. Although this evidence partly confirms that the laevorotatory mercurichloride has the α-D-manno-configuration, the α-D-gluco structure cannot as yet be excluded, except on theoretical grounds.

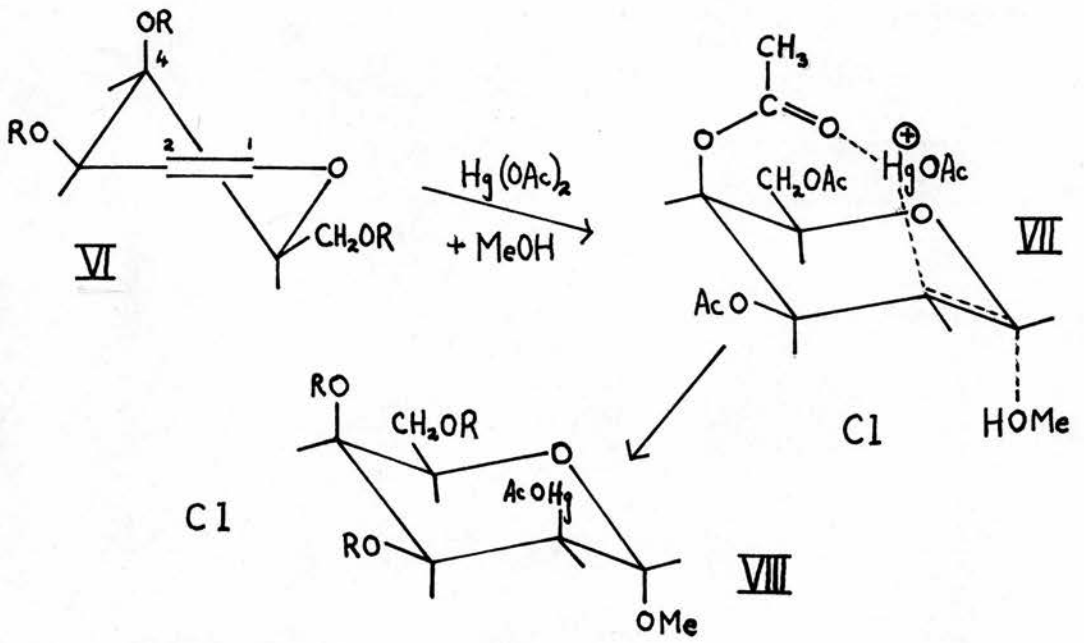
Attempts to correlate the configuration of the mercury atom in the two α-glycosidic mercurials *viz*. I; R = H, X = OAc and I; R = Ac, X = Cl by conversion of each into the other were unsuccessful.

It is interesting that, whereas D-glucal gives mainly the expected α-D-manno(?)-isomer, D-glucal triacetate (III; R = Ac) gives a high proportion (*ca*. 40%) of the β-D-gluco-isomer (V). The formation of the latter may proceed *via* a boat form[17], since



the 1C-chair transition state (IV) which fulfils the stereochemical requirements of electrophilic addition has all of the substituents axial. But an equally likely explanation of the observed behaviour is that this transition state, although disfavoured because of its 1,3-diaxial interactions, is in fact stabilised by complexing between the mercury atom and the carbonyl oxygen of the 4-acetoxy group. This type of directing effect has been postulated by Henbest and his co-workers[9] to explain their observations in methoxymercuration of cyclohexenes.

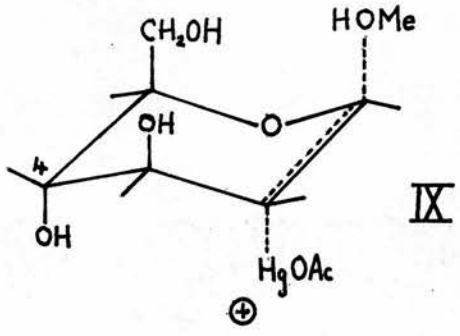
On the explanation suggested above it would be expected that mercuration of both D-galactal (VI; R = H) and its triacetate



(VI; R = Ac) should give only α-D-talo-mercuriglycosides (VIII; R = H and R = Ac, respectively), since in the galactose series the sterically favoured C1-transition state (VII) for the triacetate has

the 4-acetoxy group axial. Hence if complexing does occur, it will fix the ring in the sterically favoured chair form (C1). In fact, complexing of the type suggested might enhance the rate of mercuration of D-galactal triacetate in comparison with that of D-glucal triacetate. Work by Riddell and Schwarz[18] has shown that D-galactal triacetate reacts more than twice as fast as the glucose isomer and gives a crystalline mercurichloride (in *ca.* 90% yield), which is converted by reduction to methyl 2-deoxy- α -D-galactopyranoside.

The reason for the almost exclusive formation of the α-D-manno-mercuriglycoside from D-glucal (III; R = H) is possibly the following. Since the hydroxyl group is smaller than the acetoxy group, greater distortion of the sugar ring would be necessary to allow it to complex with the mercury atom. Inspection of models shows that the type of distortion required would force the axial groups on $C_{(3)}$ and $C_{(5)}$ in the transition state (IX) closer together, so that this effect might



IX

cancel any stabilisation achieved by complexing.

While the present work was in progress, an abstract[19] appeared in which it is stated that the methoxymercuration of D-glucal and its triacetate gives methyl 2-acetoxymercuri-2-deoxy- β -D-mannopyranoside

and the methyl 2-acetoxymercuri-2-deoxy- β -D-glucopyranoside triacetate respectively. The former conclusion appears to be incompatible with the above results.

Further investigation of carbohydrate mercurials of the type described here would clearly be of interest, both in connection with the directing effects discussed above and with regard to the preparative implications. Examples of the latter are the possibilities of synthesising α-linked disaccharides and of replacing the mercury by groups other than hydrogen.

NOTE. Most of the work described in PART II has already been published[20].

EXPERIMENTAL

1. General Information

For experimental procedures not described below see General Information in PART I.

In paper chromatography of mercury-compounds spray (d) showed them as yellow or orange spots on a pink background. The spots fluoresced strongly (yellow) in ultraviolet light, and although they were not always permanent when viewed in daylight, the fluorescence was permanent.

The α- and β-anomers of methyl 2-deoxy-D-glucopyranoside could not readily be distinguished in solvent (i), but the corresponding triacetates were clearly resolved in solvent (ii) (R_F *ca.* 0.5 and 0.4 respectively).

Although D-glucal and methyl 2-deoxy-α-D-glucopyranoside travelled at the same rate (R_F *ca.* 0.5) in solvent (i), the former could be detected in the presence of the latter, since it gave a spot instantaneously with spray (a).

The mercuric acetate used in methoxymercurations was obtained from Hopkins and Williams Ltd.; some other commercial samples smelt strongly of acetic acid.

In potassium borohydride reductions of the mercurials the deposition of finely-divided mercury was instantaneous, but the solutions were left for several hours to clear and a further quantity of borohydride was then added to check that the reduction was complete. Before acetylation, the products were evaporated repeatedly with methanol, dioxan or acetone, to remove water.

Acetylations were done in a large excess of acetic-anhydride in AnalaR pyridine. The bulk of the pyridine was evaporated off, the remainder being removed by dissolution of the resulting syrup in chloroform and extraction with N-sulphuric acid solution. The chloroform layer was then washed with aqueous sodium bicarbonate solution and dried, before being evaporated to dryness. The working-up or further treatment of the product was then continued.

2. Mercury-compounds and Associated Derivatives

(a) Methoxymercuration of D-glucal

D-Glucal[6,21,22] was made by deacetylation of D-glucal triacetate with a catalytic amount of sodium methoxide[6] in methanol. The product, which is strongly hygroscopic, was obtained as elongated prisms with m. p. 58-61° and $[\alpha]_D^{18}$ - 8.5° (c 1 in H_2O), and travelled as a single spot (R_F ca. 0.5) on paper chromatograms, using solvent (i), spray (a) or (b).

Methoxymercuration. D-Glucal (6.12 g., 41.9 mmoles) in methanol (30 ml.) was added to mercuric acetate (13.71 g., 43.0 mmoles) in methanol (150 ml.), with cooling under the tap. The optical rotation rapidly became positive and rose to a constant value within 25 min. After 1 hr. a little flocculent material was filtered off and the solution was evaporated to 60 ml. On standing, methyl 2-acetoxymercuri-2-deoxy-α-D-manno(?)pyranoside separated as shiny prisms (9.07 g., 50%), with m. p. 152.5-153° (decomp.), unchanged by recrystallisation from methanol, $[\alpha]_D^{20}$ + 18° (c 1 in MeOH), and ν_{max} 1570 and 1590 $cm.^{-1}$ (Nujol mull) [Found: C, 25.2; H, 3.7%, M (X-ray) 433. $C_9 H_{16} Hg O_7$ requires C, 24.7; H. 3.7; M, 437 . The mother-liquor yielded

identical material (1.88 g., 10%). A similar preparation, in which ethanol was added during the working up, gave 70% yield. On paper chromatograms, using solvent (i) and sprays (a) and (b), the compound streaked badly and appeared to be decomposed.

X-Ray data[16] on methyl 2-acetoxymercuri-2-deoxy- α-D-manno (?) pyranoside (kindly determined by Dr. H.W.W. Ehrlich). Orthorhombic, a = 14.3, b = 20.4, c = 8.1 Å, D_m = 2.43 (by flotation), Z = 8. Weissenberg photographs about the c-axis suggested that the compound had a very high temperature factor, which is unusual in substances that permit hydrogen-bonding. It appeared probable that the substance had a disordered structure; detailed analysis would have been very time-consuming and was not attempted.

Reduction to give methyl 2-deoxy- α-D-glucopyranoside. Potassium borohydride (130 mg., 2.4 mmoles) in N-sodium hydroxide (3.1 ml.) was added dropwise to the mercurial (4.0 g., 9.15 mmoles) in a mixture of methanol (60 ml.) and N-sodium hydroxide (11.2 ml.). Additional potassium borohydride (90 mg.) was added as a solid in three portions at intervals. 98% of the theoretical quantity of mercury was recovered and the optical rotation of the resulting solution corresponded approximately to quantitative formation of methyl 2-deoxy- α-D-glucopyranoside. Evaporation, followed by acetylation and deacetylation, yielded a syrup, which began to crystallise spontaneously. Crystallisation from acetone-dry ethyl acetate-light petroleum gave methyl 2-deoxy- α-D-glucopyranoside (1.2 g., 73%) with m. p. 89 - 91.5° and $[\alpha]_D^{20}$ + 135° (c 1 in H_2O). The mixed melting-point with a specimen prepared from 2-deoxy-D-glucose[1,2] was undepressed; this specimen had $[\alpha]_D^{20}$ + 157°

(c 1 in MeOH) and $[\alpha]_D^{22}$ +144° (c 1 in 50% aqueous MeOH). Literature values[2,6] are $[\alpha]_D$ +135° and +145° in water and methanol respectively.

Paper chromatography of the product, before acetylation, using solvent (i) and spray (a), suggested the absence of D-glucal, although in another experiment, in which less alkali was used, chromatographic evidence showed that some D-glucal was formed, presumably by elimination[8,9], and the acetylated product then had ν_{max}^{film} ca. 1650 $cm.^{-1}$ (C=C). The product obtained on deacetylation could not be crystallised.

Reduction of the reaction mixture obtained by methoxymercuration of D-glucal. D-Glucal (2,00 g., 13.7 mmoles) in methanol (15 ml.) was added to mercuric acetate (4.80 g., 15 mmoles) in methanol (30 ml.) with cooling under the tap. After 1 hr., solid mercuric acetate (0.43 g.) was added. Thirty minutes later, N-sodium hydroxide (49 ml.) was added with cooling. Potassium borohydride (0.36 g., 6.7 mmoles) in N-sodium hydroxide (7 ml.) was then added dropwise and after 5 hr. solid potassium borohydride (0.18 g.) was added. The optical rotation (+2.42°) of the resulting solution (vol. 118 ml.) was ca. 80% of the theoretical value expected for the quantitative formation of methyl 2-deoxy- α -D-glucopyranoside. Evaporation, followed by acetylation, yielded a syrup, which was shown by paper chromatography, using solvent (ii), spray (c), to contain mainly methyl 2-deoxy- α -D-glucopyranoside triacetate (R_F 0.50) together with a very small proportion of the β -anomer (R_F 0.40). The latter could not have been D-glucal triacetate, which has the same R_F-value as the α-anomer. Deacetylation of the mixture gave a syrup, which crystallised with difficulty from acetone-dry ethyl-acetate as large prisms (1.13 g.) with m. p. 75-85°.

Recrystallisation from the same solvent (proportions 1:1) yielded methyl 2-deoxy-α-D-glucopyranoside (0.78 g., 32%) with m. p. and mixed m. p. 89 - 92°.

(b) Action of methanolic hydrogen chloride on D-glucal.

Hughes, Overend and Stacey[2] obtained methyl 2-deoxy-α-D-glucopyranoside in 59% yield, by heating a solution of D-glucal in methanolic hydrogen chloride (2.5%) at 60° for 1 hr. When this preparation was repeated, using D-glucal (1.10 g., m. p. 58 - 61°) in the same reagent (28 ml.), the mobile syrup obtained could not be crystallised. Paper chromatography using solvent (i) and spray (b) showed the desired product (R_F 0.50) along with a considerable amount of fast-travelling material (R_F 0.9) and a trace of 2-deoxy-D-glucose (R_F 0.30). Using spray (a) an additional spot (R_F 0.78) was visible. The infrared spectrum of the syrup had an intense carbonyl peak, ν_{max} 1720 - 1740 $cm.^{-1}$. Distillation of the mixture at 40 - 50° (bath)/0.01 mm. gave a thick, colourless syrup (0.33 g.) as the distillate. The residue (0.72 g.) was a stiff, yellow syrup, which could not be crystallised. Paper chromatography as above, using spray (a) showed that it contained the desired glucoside, besides some 2-deoxy-sugar and a considerable amount of fast-travelling material.

(c) Characterisation of methyl 2-deoxy-α-D-glucopyranoside

Methyl 2-deoxy-α-D-glucopyranoside was sometimes found to be hard to crystallise; anhydrous conditions and slow cooling are advisable. Because of these difficulties in crystallisation, attempts

were made to obtain suitable crystalline derivatives, in addition to the 6-tosylate and 4,6-O-benzylidene-compound.

Acetylation. Only a syrup[23] was obtained when the glucoside (100 mg.) was acetylated with acetic anhydride in pyridine. The product showed only a small hydroxyl peak in the infrared spectrum, and travelled as one spot in paper chromatography using solvent (ii) and spray (c), except for a trace of the β-anomer.

Benzoylation. The glucoside (100 mg., 0.56 mmoles) was benzoylated at 0° in pyridine (1.25 ml.) and ethanol-free chloroform (1.5 ml.) by dropwise addition of benzoyl chloride (0.26 ml., 2.22 mmoles). After storage in the refrigerator for 48 hr., the excess of benzoyl chloride was decomposed by addition of water (0.12 ml.). The resulting mixture was taken up in chloroform (15 ml.) and this solution washed with N-sulphuric acid, then saturated aqueous sodium bicarbonate solution, and dried. Evaporation to dryness gave a syrup, which had no hydroxyl adsorption in the infrared region, but could be crystallised only with some difficulty. The most suitable solvent was acetone-light petroleum (1:20). The crude product (elongated prisms) had m. p. 104 - 106°. Recrystallisation from the same solvent gave methyl 2-deoxy-α-D-glucopyranoside tribenzoate (58 mg., 21%) with m. p. 105.5 - 106°, unchanged on further recrystallisation (Found: C, 68.9; H, 5.5. $C_{28}H_{26}O_8$ requires C, 68.6; H, 5.3%).

Phenylurethane. When the glucoside (50 mg., 0.28 mmoles) in dried pyridine (1.0 ml.) was treated with phenyl isocyanate (0.15 ml., 1.38 mmoles) at 95° for 75 min., then at room temperature for 20 hr.,

a crumbly, amorphous solid (190 mg.) was obtained. Crystallisation from acetone-benzene-light petroleum gave with difficulty a low yield (23 mg.) of similar material (A), with m. p. 229 - 231° (shrinking at 222 - 223°, no decomp., mixed m. p. with diphenylurea 210 - 235°). A had no hydroxyl absorption in the infrared. The mother liquor of A yielded, with difficulty, two portions of amorphous solid (40 mg. and 14 mg. respectively), which had different melting points, both lower than that of A. In view of these difficulties the phenylurethane is not a suitable derivative, and this approach was therefore abandoned.

Benzylidenation. Using the method of Hughes, Overend and Stacey[2], the deoxy-glucoside (200 mg.) was shaken with zinc chloride (250 mg.) in AnalaR benzaldehyde (1.05 ml.) for 23 hr. Some of the product had separated out as fine needles. For working up, the mixture was poured into a mixture of light petroleum and excess of saturated aqueous sodium carbonate solution (5 ml. of each), the precipitated solid being repeatedly extracted with portions (5 ml.) of boiling chloroform (50 ml. in all). The extracts yielded solid (150 mg.), which was crystallised from chloroform-light petroleum (1:4) to give long needles (110 mg., 37%) of methyl 4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside with m. p. 148 - 150° (shrinking at 146°), this being raised to 149 - 150° (shrinking at 148°) on recrystallisation from the same solvent (Found: C, 63.1; H, 6.4. Calc. for $C_{14}H_{18}O_5$ C, 63.1; H, 6.8%). The above-mentioned authors report m. p. 137 - 139°.

(d) Methoxymercuration of D-glucal triacetate

The glycal (15.00 g., 55.2 mmoles) in methanol (70 ml.) was added to mercuric acetate (18.45 g., 57.9 mmoles), which had been almost

completely dissolved in methanol (200 ml.), methanol (30 ml.) being used for washing. The reaction mixture was cooled under the tap, and no solid remained after 5 min. After a further 50 min. sodium chloride (3.55 g., 60.7 mmoles) in water (150 ml.) was added, followed by water (50 ml.). Methyl 2-chloromercuri-2-deoxy-β-D-glucopyranoside triacetate crystallised and was collected after storage overnight in the refrigerator. The needles obtained (11.33 g., 38%) had m. p. 171 - 172°. The elongated prisms obtained by recrystallisation from acetone-ethanol (1:3) had m. p. 172 - 174° and $[\alpha]_D^{18}$ + 11° (c 1 in $CHCl_3$). After two recrystallisations from the same solvent the m. p. was 173 - 174°; the optical rotation was unaltered (Found: C, 29.0; H, 4.1; Cl, 6.4. $C_{13}H_{19}ClHgO_8$ requires C, 28.9; H, 3.5; Cl, 6.6%).

Addition of ether (40 ml.) to the mother-liquor of the β-gluco-mercurial caused crystallisation. Water (50 ml.) was then added, and after storage overnight in the refrigerator elongated prisms (A, 8.21 g., 27.6%) were collected and washed with ether. They had m. p. 111 - 113° and $[\alpha]_D^{18}$ -37° (c 1 in $CHCl_3$). Recrystallisation from ethanol gave material with m. p. 112 - 114° and $[\alpha]_D^{20}$ -29° (c 1 in MeOH), which was dissolved in chloroform. After extraction of the solution with water to remove any sodium salts present, material was obtained which on crystallisation from ethyl acetate-light petroleum (1:2) gave prisms of methyl 2-chloromercuri-2-deoxy-α-D-manno(?)pyranoside triacetate with m. p. 112 - 113.5°, unchanged on recrystallisation from the same solvent, and $[\alpha]_D^{18}$ -38° (c 1 in $CHCl_3$) (Found: C, 29.0;

H, 3.9; Cl, 7.2. $C_{13}H_{19}ClHgO_8$ requires C, 28.9; H, 3.5; Cl, 6.6%). The mother-liquor of A yielded crystals (6.53 g.) with a low m. p. They were dissolved in chloroform (50 ml.) and the solution shaken with water (40 ml.) to remove sodium salts. Drying and evaporation of the chloroform gave a syrup, which on crystallisation from ethyl acetate-light petroleum (1:3, 20 ml.) yielded crystals (5.82 g., 19.5%) with m. p. 111 - 114°. Total yield 47%.

Each of the two mercurichlorides described above travelled as a single spot on paper chromatograms, using solvent (iii), spray (d), and were clearly resolved (relative R_F ca. 1.3, the β-gluco-isomer being the faster).

Reduction of the β-gluco-mercurial to give methyl 2-deoxy-β-D-glucopyranoside triacetate. Potassium borohydride (100 mg., 1.85 mmoles) in N-sodium hydroxide (7.0 ml.) was added dropwise at intervals to the mercurial (1.90 g., 3.52 mmoles) in dioxan (30 ml.) and N-sodium hydroxide (10.5 ml.). (The compound is insufficiently soluble in methanol). Additional borohydride (50 mg.) was added as a solid after 2 hr., no further darkening being observed. Evaporation, followed by acetylation and crystallisation of the product from ethanol-light petroleum gave methyl 2-deoxy-β-D-glucopyranoside triacetate (0.79 g., 74%) with m. p. 96 - 98° and $[\alpha]_D^{22}$ -24° (c 1 in $CHCl_3$), identical (mixed m. p. and infrared spectrum) with a specimen prepared as described in PART I, Experimental, 2. (f) (ii). Paper chromatography of the mother-liquor, using solvent (ii), spray (c), showed that in addition to methyl 2-deoxy-β-D-glucopyranoside

triacetate (R_F 0.37) there were at least four impurities (R_F-values 0.12, 0.20, 0.47 and 0.74), one of these being the α-anomer (R_F 0.47).

Reduction of the α-manno(?)-mercurial to give methyl 2-deoxy- α-D-glucopyranoside. Potassium borohydride (75 mg., 1.39 mmoles) in N-sodium hydroxide (4.5 ml.) was added dropwise to the mercurial (2.50 g., 4.64 mmoles) in methanol (25 ml.) and N-sodium hydroxide (18.5 ml.). Additional borohydride was added after 20 min. (75 mg.) and after 3 hr. (10 mg.), there being no sign of darkening on either occasion. The optical rotation of the solution (after being made up to 50 ml. with water) was now strongly positive (+2.29°) and corresponded to a yield of 96% of the 2-deoxy- α-glucoside, which has $[\alpha]_D$ +144° in 50% aqueous methanol. Acetylation of the product gave a syrup, which travelled as one spot in paper chromatography with solvent (ii), spray (c), except for a trace of slow-moving material (relative R_F 1.4). After deacetylation of the acetate, crystallisation from ethyl acetate-acetone gave, with difficulty, prisms of methyl 2-deoxy- α-D-gluco-pyranoside (0.12 g.) with m. p. 91 - 92°. The mother-liquor gave prisms (0.23 g.) with m. p. 88 - 91° (shrinking at 83°). Total yield 42%.

In a previous methoxymercuration using less glycal (2.50 g.) the α-manno(?)-isomer was obtained only as a colourless syrup, by concentration of the mother-liquor of the β-gluco-isomer, followed by addition of water and repeated extraction with chloroform. This syrup (3.5 g., including some solvent) travelled on chromatograms at the same rate as the authentic α-manno(?)-mercurial, and heavy spotting showed that little,

if any, of the other isomer was present. On reduction, and acetylation of the product followed by deacetylation, a syrup was obtained, which could not be crystallised, although D-glucal appeared to be absent [as indicated by the infrared spectrum of the acetate and by chromatography of the deacetylated product in solvent (i), spray (a)]. Reaction with benzaldehyde (2 ml.) and zinc chloride (0.5 g.) yielded methyl 4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (0.36 g.) with m. p. 148 - 150° (undepressed by a specimen prepared from authentic methyl 2-deoxy-α-D-glucopyranoside) and $[\alpha]_D^{19}$ +99° (c 1 in $CHCl_3$) and +83° (c 1 in EtOH). The infrared spectrum of the product was identical with that of the authentic specimen.

Reduction of the reaction mixture obtained by methoxymercuration of D-glucal triacetate. The glycal (4.00 g., 14.7 mmoles) in methanol (20 ml.) was added to a solution of mercuric acetate (4.69 g., 14.7 mmoles) in methanol (60 ml.), 10 ml. of solvent being using for washing. The optical rotation (-0.35°) of the solution (vol. 93 mls., the expansion resulting from the high concentration of solutes) was the same after reaction for 2½ hr. as after 1 hr. At 2½ hr. N-sodium hydroxide (37 ml.) was added, with cooling under the tap. A yellow colour developed. Potassium borohydride (0.20 g., 3.70 mmoles) in N-sodium hydroxide (7 ml.) was added, followed after 50 min. by a further quantity (0.14 g.) in the alkali (5 ml.). Next day the optical rotation of the solution was strongly positive (+0.98°, volume 143 ml.). Acetylation of the product and crystallisation from acetone-light petroleum, and from ethanol-light petroleum gave methyl 2-deoxy-β-D-glucopyranoside triacetate (total, 1.27 g., 28%) with m.p. 95 - 98°. Attempts to obtain the α-anomer from the deacetylated mother-liquor were unsuccessful.

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APPENDIX III

Tables of R_F-Values in Paper and Thin-layer Chromatography

In the tables which follow are collected data of R_F-values observed in the paper and thin-layer chromatography of most of the compounds described in PARTS I and II.

It was found that although the reproducibility of R_F-values was mostly quite good, it was poorer when a stationary phase had to be applied to paper, and particularly in the case of propane-1,2-diol-water. In thin-layer chromatography R_F-values were also less reproducible and varied considerably with loading, the R_F going down as loading was increased. By "reproducibility" is meant reproducibility of behaviour compared with reference substances on the same piece of paper, so that the appearance of a wide range of R_F-value in the tables does not necessarily imply corresponding unreliability. However, with the system dimethyl sulphoxide / benzene-di-isopropyl ether-dimethyl sulphoxide (5 : 5 : 1) the same substance travelled at widely varying rates, even on the same chromatogram.

When only one value of R_F is given, it means that only one determination of R_F-value was made.

Table 10 R_F-Values in Paper Chromatography

Applied Stationary Phase	Mobile Phase	Compound	Observed Range of R_F
None	Butanol-ethanol-water (4:1:5)	1,5-anhydro-D-galactitol	0.18-021
		1,5-anhydro-2-deoxy-D-lyxo-hexitol	0.35 only
		Me 2-deoxy-α-D-galactopyranoside	0.47-0.50
		Me 2-deoxy-β-D-galactopyranoside	0.38-0.43
		Me 2-deoxy-α-D-glucopyranoside	0.49-0.55
		Me 2-deoxy-β-D-glucopyranoside	0.46-0.55
		D-galactal	0.45-0.49
		D-glucal	0.52-0.55
		2-deoxy-D-galactose	0.25-0.28
		2-deoxy-D-glucose	0.28-0.31
Dimethyl sulphoxide.	Di-isopropyl ether.	Me 2-deoxy-α-D-galactopyranoside T.A.	0.50-0.58
		Me 2-deoxy-β-D-galactopyranoside T.A.	0.33-0.38
		Me 2-deoxy-α-D-glucopyranoside T.A.	0.4-0.5
		Me 2-deoxy-β-D-glucopyranoside T.A.	0.3-0.4
		D-galactal T.A.	ca. 0.3
		D-glucal T.A.	ca. 0.50
		Me 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-Ts	0.6-0.7
Dimethyl sulphoxide.	Di-isopropyl ether-benzene (1:1)	Me 2-deoxy-2-chloromercuri-α-D-manno(?) pyranoside triacetate	ca. 0.23)Relative)R_F ca.
		Me 2-deoxy-2-chloromercuri-β-D-gluco-pyranoside triacetate	ca. 0.29) 1.3.
Dimethyl sulphoxide.	Di-isopropyl ether-benzene-dimethyl sulph-oxide (5:5:1)	Me 2-deoxy-α-D-galactopyranoside 6-Ts	0.4-0.5
		Me 2-deoxy-α-D-glucopyranoside 6-Ts	ca. 0.2
			Range of R_{MT}
Propane-1,2-diol-water (4:1)	Chloroform-benzene (1:1)	1,5-anhydro-D-galactitol 6-Ts	0.33-0.39
		1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-Ts	2.1
		Me 2-deoxy-α-D-galactopyranoside 6-Ts	2.6-5.4 (R_F 0.15-0.2)
		Me 2-deoxy-α-D-glucopyranoside 6-Ts	2.6 (R_F 0.35)
		Me α-D-galactopyranoside 6-Ts	0.9 (R_F 0.12)
		Me β-D-galactopyranoside 6-Ts	0.9
		Me α-D-glucopyranoside 6-Ts	0.8

T.A.= triacetate

Me = methyl Ts = tosylate R_{MT} = distance travelled relative to methyl α-D-mannopyranoside 3-Ts

Table 11. R_F-Values in Thin-layer Chromatography (Silica)

Applied Stationary Phase	Mobile Phase	Compound	Observed Range of R_F
None	Ethyl acetate	1,5-anhydro-D-galactitol 6-Ts	0.08-0.13
		1,5-anhydro-2-deoxy-D-lyxo-hexitol 6-Ts	0.39
		Me 2-deoxy-α-D-galactopyranoside 6-Ts	0.47-0.60
		Me 2-deoxy-β-D-galactopyranoside 6-Ts	0.53-0.55
		Me 2-deoxy-α-D-glucopyranoside 6-Ts	0.53-0.67
		Me 2-deoxy-β-D-glucopyranoside 6-Ts	0.43-0.45
		Me α-D-galactopyranoside 6-Ts	0.07
		Me 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-Ts	0.8-0.9
		1,5-anhydro-D-glucitol 6-Ts	0.12
None	Benzene-ether (1:1)	Me 2-deoxy-α-D-galactopyranoside 6-Ts	0.05-0.1
		Me 2-deoxy-β-D-galactopyranoside 6-Ts	0.06-0.07
		Me 2-deoxy-α-D-glucopyranoside 6-Ts	0.07
		Me 2-deoxy-β-D-glucopyranoside 6-Ts	0.04
		Me 2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside 6-Ts	0.7-0.8
Water	Butanol-ethanol-water (4:1:5)	1,2-O-ethylene-β-D-glucopyranose	0.31-0.38

Me = methyl Ts = tosylate

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190. *The Methoxymercuration of* D-*Glucal and Tri*-O-*acetyl*-D-*glucal: a New Route to 2-Deoxyglycopyranosides.*

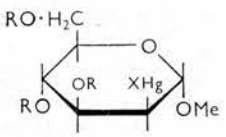
By G. R. Inglis, J. C. P. Schwarz, and (in part) Lilian McLaren.

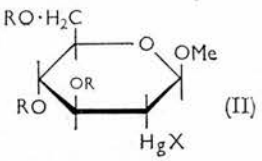
Methoxymercuration of D-glucal gives mainly methyl 2-acetoxymercuri-2-deoxy-α-D-manno(?)pyranoside. Tri-*O*-acetyl-D-glucal yields methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside and a syrup, probably the α-D-manno-isomer. Reduction of the mercurials gives the corresponding 2-deoxyglucopyranosides in good yield.

The work described here was undertaken in search of better methods for the preparation of the methyl 2-deoxy-α- and -β-D-glucopyranosides, which were required in another investigation. Both compounds have previously been prepared from D-glucal, through 2-deoxy-D-glucose, by two-stage [1,2] and five-stage [3] syntheses, respectively, the overall yields being *ca.* 20% and *ca.* 15%. A four-stage synthesis of the β-anomer from tri-*O*-acetyl-D-glucal with an overall yield of *ca.* 10% has also been described.[4] A major factor limiting the yields in syntheses by way of 2-deoxy-D-glucose is that the hydration of D-glucal to this compound is complicated by the formation of an unsaturated by-product.[5] Despite a report [2] that methyl 2-deoxy-α-D-glucopyranoside can be obtained in 59% yield by the acid-catalysed addition of methanol to D-glucal, this reaction gave unpromising results in our hands; chromatographic evidence showed the presence of the desired compound but by-products prevented its crystallisation. It has already been noted [6] that large amounts of a furan derivative are produced when this reaction is carried out under milder conditions.

In view of the complications which seem to beset acid-catalysed additions to D-glucal, it appeared profitable to investigate indirect methods of adding the elements of methanol to the double bond, *e.g.*, methoxymercuration [7,8] followed by reduction [·CH:CH· ⟶ ·CH(Hg·OAc)·CH(OMe)· ⟶ ·CH_2·CH(OMe)·]. Since the methoxymercuration of D-glucal can be regarded [7,8,9] as a typical electrophilic addition to a vinyl ether, it was expected that the mercury atom and the methoxyl group would become attached to $C_{(2)}$ and $C_{(1)}$, respectively, and that *trans*-addition would occur.* Hence the most likely products are methyl 2-acetoxymercuri-2-deoxy-α-D-mannopyranoside (I; R = H, X = OAc) and the β-D-gluco-isomer (II; R = H, X = OAc). The former compound

(I)





(II)

might be expected to predominate, since it would be formed by diaxial addition [12] to the most stable half-chair conformation [13] of D-glucal ($C_{(6)}$ and $O_{(4)}$ equatorial, $O_{(3)}$ quasi-equatorial).

In fact, optical-rotation measurements showed that D-glucal reacted rapidly with mercuric acetate in methanol, and a crystalline methoxymercuriacetate was isolated in 60—70% yield. On reduction with potassium borohydride in the presence of alkali, this gave methyl 2-deoxy-α-D-glucopyranoside which was freed from borate by acetylation.[14] The configuration at $C_{(1)}$ in the mercuriacetate is therefore established and, if *trans*-addition is assumed, the compound must be methyl 2-acetoxymercuri-2-deoxy-α-D-mannopyranoside (I; R = H, X = OAc), the isomer expected on conformational grounds. To confirm this, Dr. H. W. W. Ehrlich kindly undertook an *X*-ray examination of the compound.

* A contrary view of methoxymercuration has been expressed by Wright and his co-workers,[10] who have pointed out that earlier *X*-ray evidence [11] for the occurrence of *trans*-addition in the methoxymercuration of cyclohexene is inconclusive.

Unfortunately, this proved unpromising (see Experimental section). Attempts were made to prepare the corresponding mercurichloride and mercuribenzoate in the hope that these compounds might be more suitable for *X*-ray structure determination; however, only syrups were obtained when a solution of the mercuriacetate in methanol was percolated through a column of Amberlite IRA-400 resin in the chloride or benzoate form.

The procedure described above provides a convenient route to methyl 2-deoxy-α-D-glucopyranoside, the overall yield from D-glucal being 45—50%. When the reduction was carried out without prior isolation of the mercuriacetate, the overall yield was 32%. Paper chromatography and optical rotations indicated that only a small proportion of methyl 2-deoxy-β-D-glucopyranoside was formed in the latter reduction, showing that the methoxymercuration is highly stereospecific.

The reaction of tri-*O*-acetyl-D-glucal with mercuric acetate in methanol was also studied. The syrupy product was clearly a mixture and, although a solid mercuriacetate could be obtained from it, it was more convenient to replace the ionic acetate by chloride. This yielded a crystalline mercurichloride (38% yield) and a syrupy residue which failed to crystallise.* An *X*-ray structure analysis, kindly undertaken by Dr. H. W. W. Ehrlich,[15] showed that the crystalline compound was methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside (II; R = Ac, X = Cl). This agrees with the assumption made earlier that methoxymercuration is a *trans*-addition. Reductive demercuration of the crystalline mercurichloride with potassium borohydride in the presence of alkali was accompanied by deacetylation and yielded methyl 2-deoxy-β-D-glucopyranoside, which was isolated as the triacetate. This confirms the stereochemistry at $C_{(1)}$ and constitutes a convenient preparation of methyl 2-deoxy-β-D-glucopyranoside, the overall yield of the triacetate from tri-*O*-acetyl-D-glucal being 28%.

Reduction of the syrupy residue from the crystalline mercurichloride was again accompanied by deacetylation, and optical-rotation measurements and paper chromatography suggested that the product was mainly methyl 2-deoxy-α-D-glucopyranoside together with a little of the β-anomer. The former was isolated as the 4,6-*O*-benzylidene compound;[2] we have confirmed that the triacetate is a syrup.[16] The above evidence suggests that the syrupy mercurichloride is mainly methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-α-D-mannopyranoside (I; R = Ac, X = Cl), although the α-D-*gluco*-configuration cannot be excluded except on theoretical grounds.

It is interesting that, whereas D-glucal gives mainly the expected α-D-*manno*-isomer, tri-*O*-acetyl-D-glucal gives a high proportion of the β-D-*gluco*-isomer. Detailed discussion of this difference is postponed until further work, particularly in the galactose series, is complete. The formation of the β-D-*gluco*-isomer may proceed through a boat form[17] since the chair intermediate which fulfils the stereochemical requirements of electrophilic addition has all the substituents axial (the latter conformation may, however, be stabilised by complex-formation between the mercury atom and the 4-acetoxy-group, as postulated by Henbest and his co-workers[8]).

While the present work was in progress, an abstract[18] appeared in which it is stated that methoxymercuration of D-glucal and its triacetate gives methyl 2-acetoxymercuri-2-deoxy-β-D-mannopyranoside and the methyl 2-acetoxymercuri-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside, respectively. The former conclusion appears to be incompatible with our results.

Methyl tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside has also been obtained by addition of hydrogen bromide to tri-*O*-acetyl-D-glucal[19] followed by reaction of the crude product with methanol and silver carbonate; this procedure gave a lower yield (*ca.* 20%) than the mercuration route and is also less convenient.

* [*Added in Proof, January 23rd*, 1962.—In a later experiment, the second isomer crystallised spontaneously (47% yield, m. p. 111—113°) on addition of ether to the mother liquor from the β-D-gluco-compound. After crystallisation from ethyl acetate–light petroleum, it had m. p. 112—114°, $[\alpha]_D$ −37° (*c* 1 in $CHCl_3$) (Found: C, 29·0; H, 4·0; Cl, 7·2. $C_{13}H_{19}ClHgO_8$ requires C, 28·9; H, 3·5; Cl, 6·6%). Reduction in the manner described for the syrup gave crystalline methyl 2-deoxy-α-D-glucopyranoside].

Experimental

Paper chromatography (descending) was done on Whatman No. 1 paper with the following solvent systems: (i) butanol–ethanol–water (4 : 1 : 5, upper layer); (ii) dimethyl sulphoxide as stationary phase and di-isopropyl ether as mobile phase;[20] (iii) dimethyl sulphoxide as stationary phase and di-isopropyl ether–benzene (1 : 1) as mobile phase. Sprays were: (*a*) sodium periodate–potassium permanganate;[21] (*b*) 2% sodium periodate solution followed by *p*-nitroaniline;[22] (*c*) 0·1N-sodium hydroxide in 50% ethanol, followed after 10 min. by treatment (*b*); (*d*) 0·04% of Rhodamine 6G[23] in ethanol, preceded by one or two immersions of the paper in a saturated solution of iodine in light petroleum (this treatment revealed the mercurichlorides as yellow spots on a pink background; the spots fluoresced strongly in ultraviolet light). When dimethyl sulphoxide was used as stationary phase, the papers were heated at 125° for 10 min. before spraying. The α- and the β-anomer of methyl 2-deoxy-D-glucopyranoside could not be readily distinguished in solvent (i), but the corresponding triacetates were clearly resolved in solvent (ii) (R_F *ca.* 0·50 and 0·42, respectively). Although D-glucal and methyl 2-deoxy-α-D-glucopyranoside travelled at the same rate (R_F *ca.* 0·5) in solvent (i), the former could be detected in presence of the latter, since it gave an instantaneous spot with spray (*a*).

Evaporations were carried out under reduced pressure at 40° or below, usually on a rotatory evaporator. Optical rotations were measured in a 1-dm. tube, and infrared spectra were obtained with a Perkin–Elmer model 137 Infracord spectrophotometer. Methanol used in methoxymercurations and deacetylations was dried according to Vogel's directions.[24] The light petroleum used had b. p. 60—80°.

Methoxymercurations.—Mercuric acetate was obtained from Hopkin and Williams Ltd.; some other commercial samples smelt strongly of acetic acid.

Methoxymercuration of D-*Glucal.*—D-Glucal (6·12 g., 41·9 mmoles) in methanol (30 ml.) was added to mercuric acetate (13·71 g., 43·0 mmoles) in methanol (150 ml.) with cooling under the tap. The optical rotation rapidly became positive and rose to a constant value within 25 min. After 1 hr., a little flocculent material was filtered off and the solution was evaporated to 60 ml. *Methyl 2-acetoxymercuri-2-deoxy-α-*D-*manno(?)pyranoside* (I; R = H, X = OAc) gradually separated as prisms (9·07 g., 50%), m. p. 152·5—153° (decomp.), unchanged by crystallisation from methanol, $[\alpha]_D^{20}$ +18° (*c* 1 in MeOH) $\nu_{max.}$ 1570 and 1590 cm.$^{-1}$ (in Nujol) [Found: C, 25·2; H, 3·7%; *M* (*X*-ray), 433. $C_9H_{16}HgO_7$ requires C, 24·7; H, 3·7%; *M*, 437]. The mother-liquor yielded identical material (1·88 g., 10%). A similar preparation in which ethanol was added during the working-up gave 70% yield.

X-*Ray data on methyl 2-acetoxymercuri-2-deoxy-α-*D-*manno(?)pyranoside* (kindly determined by Dr. H. W. W. Ehrlich). Orthorhombic, a = 14·3, b = 20·4, c = 8·1 Å, D_m = 2·43 (by flotation), Z = 8. Weissenberg photographs about the c-axis suggested that the compound had a very high temperature factor, which is unusual in substances that permit hydrogen-bonding. It appeared probable that the substance had a disordered structure; detailed analysis would have been very time-consuming and was not attempted.

*Methoxymercuration of Tri-*O*-acetyl-*D*-glucal.*—The glycal (2·50 g., 9·2 mmoles) in methanol (10 ml.) was added to mercuric acetate (3·07 g., 9·6 mmoles) in methanol (35 ml.). After 2 hr., sodium chloride (0·565 g., 9·65 mmoles) in water (10 ml.) was added, followed by water (20 ml.). *Methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-*β*-*D*-glucopyranoside* (II; R = Ac, X = Cl) crystallised and was collected after storage in the refrigerator overnight. The prisms (1·90 g., 38·5%) had m. p. 172—174°, $[\alpha]_D^{18}$ +11° (*c* 1 in $CHCl_3$), unchanged by crystallisation from ethanol–acetone (Found: C, 29·0; H, 4·1; Cl, 6·4. $C_{13}H_{19}ClHgO_8$ requires C, 28·9; H, 3·5; Cl, 6·6%). The mother-liquor was concentrated, dioxan (20 ml.) being added to reduce frothing, and extracted three times with chloroform after addition of water. The extract, which had a negative optical rotation, was evaporated to a syrup [A; probably methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-α-D-manno(?)pyranoside] (3·5 g.) which still contained some solvent.

The two mercurichlorides were clearly resolved on chromatography in solvent (iii) (spray *d*); heavy spotting revealed that the syrup A contained little, if any, of the faster-moving crystalline mercurichloride (relative R_F *ca.* 1·3).

Reductions of the Mercurials by Potassium Borohydride.—In these, the deposition of finely divided mercury was instantaneous, but the solutions were left for several hours to clear and a further quantity of borohydride was then added to check that the reduction was complete.

Before acetylation, the products were evaporated repeatedly with methanol, dioxan, or acetone to remove water. Acetylations were done with a large excess of acetic anhydride in " AnalaR " pyridine, and the products were worked up by addition of water and extraction with chloroform. Deacetylations were carried out with a catalytic quantity of sodium methoxide in methanol; after being kept overnight, the solutions were neutralised with Amberlite IRC-50.

Methyl 2-deoxy-α-D-glucopyranoside from methyl 2-acetoxymercuri-2-deoxy-α-D-manno(?)-pyranoside. Potassium borohydride (0·13 g., 2·4 mmoles) in N-sodium hydroxide (3·1 ml.) was added dropwise to the mercurial (4·0 g., 9·15 mmoles) in a mixture of methanol (60 ml.) and N-sodium hydroxide (11·2 ml.). Additional potassium borohydride (0·09 g.) was added as a solid in three portions at intervals. 98% of the theoretical quantity of mercury was recovered and the optical rotation of the resulting solution corresponded approximately to quantitative formation of methyl 2-deoxy-α-D-glucopyranoside. Evaporation, followed by acetylation and deacetylation, yielded a syrup which began to crystallise spontaneously. Crystallisation from dry ethyl acetate–acetone–light petroleum gave methyl 2-deoxy-α-D-glucopyranoside (1·2 g., 73%), m. p. 89—91·5°, $[\alpha]_D^{20}$ +135° (*c* 1 in H_2O). The mixed m. p. with a specimen prepared from 2-deoxy-D-glucose [1,2] was undepressed; this specimen had $[\alpha]_D^{20}$ +157° (*c* 1 in MeOH) and $[\alpha]_D^{22}$ +144° (*c* 1 in 50% aqueous MeOH). Recorded values [2,6] are $[\alpha]_D$ +135° and +145° in water and methanol, respectively.

Chromatography [solvent (i), spray (*a*)] of the product before acetylation suggested the absence of D-glucal, although in another experiment in which less alkali was used chromatographic evidence showed that some D-glucal was formed, presumably by elimination; [7,8] the acetylated product, as a film, then had $\nu_{max.}$ *ca.* 1650 cm.$^{-1}$ (C=C), and the deacetylated product did not crystallise. Methyl 2-deoxy-α-D-glucopyranoside is sometimes difficult to crystallise; anhydrous conditions and slow cooling are advisable.

Methyl 2-deoxy-β-D-glucopyranoside triacetate from methyl 3,4,6-tri-O-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside. Potassium borohydride (0·10 g., 1·85 mmoles) in N-sodium hydroxide (7·0 ml.) was added dropwise at intervals to the mercurial (1·90 g., 3·52 mmoles) in dioxan (30 ml.) and N-sodium hydroxide (10·5 ml.). Additional borohydride (0·05 g.) was added as a solid after 2 hr., no further darkening being observed. Evaporation followed by acetylation and crystallisation of the product from ethanol–light petroleum gave methyl 2-deoxy-β-D-glucopyranoside triacetate (0·79 g., 74%), m. p. 96—98°, $[\alpha]_D^{22}$ −24° (*c* 1 in $CHCl_3$), identical (mixed m. p. and infrared spectrum) with a specimen prepared as described below. Fischer, Bergmann, and Schotte [4] give m. p. 96—97°, $[\alpha]_D^{19}$ −30° in tetrachloroethane. Chromatography [solvent (ii), spray (*c*)] of the mother-liquor showed that at least three by-products were formed.

Reduction of the syrup A. Potassium borohydride (0·15 g., 2·78 mmoles) in N-sodium hydroxide (6·9 ml.) was added dropwise at intervals to the syrup (2·5 g., <4·6 mmoles) in methanol (30 ml.) and N-sodium hydroxide (14 ml.). The optical rotation of the solution became strongly positive (1·50°; volume 55 ml.). Evaporation and acetylation yielded a syrup. Chromatography [solvent (ii), spray (*c*)] gave a large spot travelling at the same rate as authentic methyl 2-deoxy-α-D-glucopyranoside triacetate and a trace corresponding to the β-anomer. Deacetylation gave a syrup and, although D-glucal appeared to be absent [as indicated by the infrared spectrum of the acetate and by chromatography of the deacetylated product in solvent (i)], this did not crystallise. Reaction with benzaldehyde (2 ml.) and zinc chloride (0·5 g.) yielded methyl 4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (0·36 g.), m. p. 148—150°, undepressed by a specimen prepared from authentic methyl 2-deoxy-α-D-glucopyranoside. The authentic benzylidene compound had m. p. 149—150° (Found: C, 63·1; H, 6·4. Calc. for $C_{14}H_{18}O_5$: C, 63·1; H, 6·8%). Hughes, Overend, and Stacey [2] give m. p. 137—139°.

Reduction of the reaction mixture obtained by methoxymercuration of D-glucal. D-Glucal (2·0 g., 13·7 mmoles) in methanol (15 ml.) was added to mercuric acetate (4·80 g., 15 mmoles) in methanol (30 ml.) with cooling under the tap. After 1 hr., solid mercuric acetate (0·43 g.) was added. Thirty minutes later, N-sodium hydroxide (49 ml.) was added with cooling. Potassium borohydride (0·36 g., 6·7 mmoles) in N-sodium hydroxide (7 ml.) was then added dropwise. After 5 hr., solid potassium borohydride (0·18 g.) was added. The optical rotation of the resulting solution was *ca.* 80% of the theoretical value expected for the quantitative formation of methyl 2-deoxy-α-D-glucopyranoside. Evaporation, followed by acetylation, yielded a syrup which was shown by chromatography [solvent (ii), spray (*c*)] to contain mainly

methyl 2-deoxy-α-D-glucopyranoside triacetate with a very small proportion of the β-anomer. Deacetylation gave a syrup which crystallised from dry ethyl acetate–acetone (m. p. 75—85°; 1·13 g.). Recrystallisation yielded methyl 2-deoxy-α-D-glucopyranoside (0·78 g., 32%), m. p. and mixed m. p. 89—92°.

Methyl 2-Deoxy-β-D-glucopyranoside Triacetate from Tri-O-acetyl-D-glucal through the Aceto-bromo-compound.—Hydrogen bromide [25] (6 g., 74 mmoles; freed from bromine by bubbling through phenol in carbon tetrachloride) in dried benzene (65 ml.) was added to tri-*O*-acetyl-D-glucal (10 g., 37 mmoles) in benzene (35 ml.) containing benzoyl peroxide (0·09 g.), the mixture being cooled under the tap. After 50 min. the solution had a high positive optical rotation (25·4°, *i.e.*, $[\alpha]_D$ *ca.* +200°). It was then concentrated at 30° to a pale yellow, mobile syrup which was evaporated with benzene. The product was immediately dissolved in methanol (75 ml.), and silver carbonate (15 g.) was added in portions. After being kept overnight, the mixture was filtered and concentrated. Crystallisation from acetone–light petroleum, ether–light petroleum, and ethanol–light petroleum gave (with some difficulty) methyl 2-deoxy-β-D-glucopyranoside triacetate (2·23 g., 20%), m. p. 93—96°, which after further crystallisation had m. p. 96—98°, $[\alpha]_D^{18}$ −24° (*c* 1·5 in $CHCl_3$). Deacetylation gave methyl 2-deoxy-β-D-glucopyranoside, m. p. 121—122°, $[\alpha]_D^{17}$ −48° (*c* 1 in H_2O). Fischer, Bergmann, and Schotte [4] give m. p. 121—122°, $[\alpha]_D^{17}$ −48° (in water).

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